

**AN ANALYSIS OF AUDITORY FUNCTIONING AND  
CAPABILITIES OF CHILDREN WITH HIV LIVING IN LOW SOCIO-  
ECONOMIC COMMUNITIES**

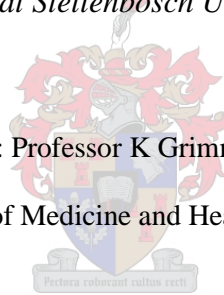
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## Declaration

By submitting this dissertation electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the sole author thereof (save to the extent explicitly otherwise stated), that reproduction and publication thereof by Stellenbosch University will not infringe any third party rights and that I have not previously in its entirety or part submitted it for obtaining any qualification.

This dissertation includes two original articles published in peer-reviewed journals and three unpublished papers submitted to peer-reviewed journals. The development and writing of the papers (published and unpublished) were the principal responsibility of myself and, for each of the papers where this is not the case, a declaration is included in the dissertation indicating the nature and extent of the contributions of co-authors.

These papers are listed in full below.

### Chapter 3:

Dawood, G., Klop, D., Olivier, O., Elliott, H., Pillay, M., & Grimmer, K. (2020). Nature and extent of hearing loss in HIV-infected children: A scoping review. *International Journal of Pediatric Otorhinolaryngology*.  
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### Chapter 4:

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**Appendix B:**

Dawood, G., Klop, D., Pillay, M., & Grimmer, K. (submitted: 19 August 2019). HIV, hearing loss, and learning capacity in Cape Metropole pre-teens, South Africa: A cross-sectional study. *BMC Pediatrics*.

**Appendix C:**

Dawood, G., Klop, D., Pillay, M., & Grimmer, K. (submitted: 17 October 2019). Auditory processing and learning capacity in 9 to 12-year-old children from Cape Town, South Africa: A cross-sectional study. *PLOS ONE*

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2. no other authors contributed to *chapter 3 in the dissertation* besides those specified above, and
3. potential conflicts of interest have been revealed to all interested parties and that the necessary arrangements have been made to use the material in *chapter 3 in the dissertation*.

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2. no other authors contributed to *chapter 4 in the dissertation* besides those specified above, and
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## **Abstract**

### **Background**

Antiretroviral treatment (ART) has reduced opportunistic infections and enabled children living with HIV (CLHIV) to develop similarly to their peers who are HIV negative. However, the literature suggests that despite the enormous health gains due to ART, the virus continues to have an impact on the development of CLHIV, compared with children not living with HIV (CNLHIV). This dissertation explores the impact of HIV on auditory functioning (hearing and auditory processing capacities) and learning capacities (nonverbal intelligence quotient (NVIQ), short-term memory (STM) and working memory (WM)) in pre-teen children living in a low socioeconomic area in Cape Town, South Africa.

Specifically, this study:

- Described a profile of hearing in CLHIV and CNLHIV;
- Described a profile of auditory processing capacities in CLHIV and CNLHIV;
- Investigated the predictor variables associated with hearing loss in CLHIV;
- Tested the association between auditory functioning and learning capacities in CLHIV and CNLHIV.

### **Method**

This dissertation reports a cross-sectional investigation into 55 participants, aged 9- to 12-year olds, recruited from a low socioeconomic demographic catchment area, of one large metropolitan South African public tertiary hospital. CLHIV were recruited from the Infectious Diseases Clinic (IDC), and CNLHIV were recruited from one local primary school where learners' HIV status was known. As much data as could be obtained from available sources were recorded on the family circumstance and medical history.

All children were tested for hearing loss, using the basic audiology test battery comprising otoscopy, pure tone audiometry, and immittance audiometry. All children were



also tested using the Test of Nonverbal Intelligence Fourth Edition (TONI 4). Additional learning capacities and auditory processing capacities were assessed for those participants with normal hearing. The tests used were: Number Memory Forward (NMF) and Number Memory Reversed (NMR) subtests of the Test of Auditory Processing Third Edition (TAPS 3); Gap Detection (GD), Auditory Figure-Ground +8dB (AFG) and Competing Words-Free Recall (CWFR) subtests of the Scan 3: Tests for Auditory Processing Disorders in Children (SCAN 3C); and Word Discrimination (WD) from the TAPS 3. Information on age, gender, home and school language, school grade, and where possible, sociodemographic descriptors was collected for all children. Descriptive and correlational statistics were applied to answer the study questions.

## **Results**

There was a low response rate to recruitment, with only 23 CLHIV (20.9% invited CLHIV) and 32 CNLHIV (19.7% invited CNLHIV) being enrolled. The primary language spoken at home was Afrikaans (46.4%), and English and African languages (26.8%) were equally represented. Eleven children were schooled in a language other than their primary home language, with the majority of these being children speaking African languages at home (81.8%). Hearing loss prevalence was 66.7% for CLHIV and 33.3% for CNLHIV. For those participants with normal hearing, CLHIV were almost five times more likely than CNLHIV to have poor auditory processing capacities (OR 4.95 (95%CI 1.24-19.69). Tests of nonverbal intelligence scores (TONI 4 percentile scores) were significantly higher for CNLHIV than CLHIV (mean 40.6% (SD 19.2); mean 20.4% (SD 10.1) respectively) (OR 4.3 (95%CL 1.0-23.4)). Hearing loss was not associated with TONI 4 percentile scores (OR 0.9 (95%CL 0.3-3.5)). Testing for confounders was constrained due to inadequate data.

## **Conclusion**

The findings add to the scarce body of knowledge about auditory processing and learning capacities of children living with chronic HIV. These skills appear to be significantly poorer in CLHIV than CNLHIV. Ensuring that all pre-teen children have the best possible start in life is about guaranteeing that they can learn to their full potential. Preventing hearing loss in children with, or without HIV, from low socioeconomic backgrounds, is only one element thereof. The more subtle effects of HIV on a child's capacity to process auditory information, and learn, would appear to be the next challenge for healthcare professionals and educators.

## **Opsomming**

### **Agtergrond**

Antiretrovirale terapie (ART) het opportunistiese infeksies in kinders wat met MIV saamleef verminder en hul in staat gestel om soos hul MIV-negatief portuurgroep te ontwikkel. Vanuit die literatuur blyk dit egter dat, ten spyte van die groot gesondheidsvoordele teweeggebring deur ART, daar steeds 'n impak is op die wyse wat kinders wat met MIV saamleef kognitief ontwikkel in vergelyking met kinders wat MIV-negatief is. Hierdie tesis het die impak van MIV op ouditiewe funksionering (gehoorverlies, ouditiewe prosessering) en sekere ander vermoëns om te leer (nieverbale intelligensiekwasiënt, korttermyngeheue en werkgeheue in pre-tiener kinders afkomstig uit 'n laer sosio-ekonomiese area in Kaapstad, Suid-Afrika, verken. Hierdie studie het spesifiek:

- Die gehoorprofiel van kinders wat met en sonder MIV saamleef beskryf;
- Die ouditiewe prosesseringsprofiel van kinders wat met en sonder MIV saamleef beskryf;
- Die voorspellingsveranderlikes geassosieer met gehoorverlies in kinders wat met MIV saamleef ondersoek;
- Die assosiasie tussen ouditiewe funksionering en leervermoë van kinders wat met en sonder MIV saamleef, getoets

### **Metode**

Hierdie proefskrif rapporteer 'n dwarsdeursnit ondersoek na 55 deelnemers, ouderdom 9 tot 12-jaar, wat gewerf is uit 'n laer sosio-ekonomiese opvangsgebied van een groot metropolitaanse openbare tersiêre hospitaal in Suid-Afrika. Kinders wat met MIV saamleef is gewerf by die hospitaal se Kliniek vir Infektiewe Siektes en ongeïnfekteerde kinders is gewerf by 'n plaaslike laerskool waar kinders se MIV status bekend was. Soveel moontlike

data is verkry uit beskikbare bronne met betrekking tot gesinsomstandighede, akademiese vordering en mediese geskiedenis.

Alle kinders is getoets vir gehoorverlies deur middel van die basiese oudiometriesse toetsbattery bestaande uit otoskopie, suiwertoon oudiometrie en imitansieoudiometrie. Alle kinders is ook getoets vir leervermoë met behulp van die Test of Nonverbal Intelligence Fourth Edition (TONI 4). Bykomende toetsing is gedoen vir kinders met normale gehoor: bykomende aspekte van leervermoë is getoets met behulp van die Number Memory Forward en Number Memory Reversed subtoetse van die Test of Auditory Processing Third Edition (TAPS 3). Ouditiewe prosesseringsvaardighede is getoets deur middel van drie subtoetse van die Scan 3: Tests for Auditory Processing Disorders in Children (Scan 3C); naamlik Gap Detection (GD), Auditory Figure Ground +8dB (AFG), Competing Words-Free Recall (CWFR), asook een subtoets van die TAPS 3 (Word Discrimination). Inligting oor al die kinders met betrekking tot ouderdom, geslag, huis- en skooltaal, skoolvlak, en waar moontlik, sosio-demografiese beskrywings, is verkry. Beskrywende en korrelasie statistiek is gebruik om die navorsingsvrae te beantwoord.

## **Resultate**

Daar was 'n swak respons op werwingspogings en slegs 23 kinders wat met MIV saamleef (20.9% van kinders in dié groep wat uitgenooi is) en 32 kinders wat nie met MIV saamleef nie (19.7% van kinders in dié groep wat uitgenooi is) ingesluit in die studie. Die primêre huistaal van deelnemers was Afrikaans (46.4%), Engels (26.8%) en Afrika-tale (26.8%). Elf kinders het skoolonderrig in 'n ander taal as hul huistaal ontvang, en die meerderheid van hierdie kinders was moedertaalsprekers van 'n Afrika-aal (81.8%). Die prevalensie van gehoorverlies was 66.7% vir kinders wat met MIV saamleef en 33.3% vir kinders wat nie met MIV saamleef nie. Vir deelnemers met normale gehoor, was kinders wat met MIV saamleef ongeveer vyf keer meer geneig om swak ouditiewe

prosesseringsvaardighede te hê as kinders sonder MIV (kansverhouding 4.95 (95% vertrouensinterval 1.24-19.69). Tellings van nie-verbale intelligensietoetse (TONI 4 persentietellings) was beduidend hoër vir kinders sonder MIV as vir kinders wat met MIV saamleef (gemiddeld 40.6% (SA 19.2); gemiddeld 20.4% (SA 10.1) onderskeidelik) (kansverhouding 4.3 (95% vertrouensvlak 1.0-23.4)). Gehoorverlies het geen verskil aan TONI 4 persentietellings gemaak nie (kansverhouding 0.9 (95% vertrouensvlak 0.3-3.5)). Toetsing vir strengelveranderlikes was beperk weens onvoldoende data-insameling.

### **Gevolgtrekking**

Bevindinge dra by tot die beperkte kennis oor ouditiewe prosesseringsvaardighede en die vermoë om te leer in kinders wat met chroniese MIV saamleef. Hierdie vaardighede het beduidend swakker voorgekom as in kinders wat MIV-negatief is. Om te verseker dat alle pre-tiener kinders die beste moontlike voorsprong in die lewe het, moet hulle potensiaal om te leer na die beste van hul vermoëns verseker word. Die voorkoming van gehoorverlies in kinders met of sonder MIV, wat afkomstig is uit laer sosio-ekonomiese omstandighede, is slegs een faktor. Die meer subtiele implikasies van saamleef met MIV op kinders se vermoë om ouditief te prosesseer en te leer, is waarskynlik die volgende uitdaging vir gesondheidswerkers en opvoeders.

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### **List of Abbreviations**

AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral treatment / therapy
ARV	Antiretroviral drug
HIV	Human Immunodeficiency Virus
CLHIV	Children living with HIV
CNLHIV	Children not living with HIV
CNS	Central nervous system
HAART	Highly active antiretroviral treatment
HAND	HIV-associated neurocognitive disorder
MTCT	Mother-to-Child Transmission
NVIQ	Nonverbal intelligence quotient
PLHIV	People living with HIV
PMTCT	Prevention of Mother-to-Child Transmission
PTA	Pure tone average
TAPS 3	Test of Auditory Processing Third Edition
TB	Tuberculosis
TONI 4	Test of Nonverbal Intelligence Fourth Edition
SCAN-3C	SCAN 3 for Children: Tests of Auditory Processing Disorders Third Edition
SDG 4	Sustainable development goal 4
STM	Short-term memory
WM	Working memory

## List of Terms

***Acquired Immune Deficiency Syndrome (AIDS):*** A disease of the immune system due to infection with HIV. Acquired immunodeficiency syndrome (AIDS) is the most advanced stage of HIV infection (AIDSinfo, 2018, p.2).

***Adherence:*** Taking medications (or other treatment) exactly as instructed by a health care provider (AIDSinfo, 2018, p.4).

***Antiretroviral drugs (ARVs):*** A drug used to prevent a retrovirus, such as HIV, from replicating. The term primarily refers to antiretroviral (ARV) HIV drugs (AIDSinfo, 2018, p.10).

***Antiretroviral treatment/therapy (ART):*** The daily use of a combination of HIV medicines (called an HIV regimen) to treat HIV infection. A person's initial HIV regimen generally includes three antiretroviral (ARV) drugs from at least two different HIV drug classes (AIDSinfo, 2018, p.10). The terms ART and highly active (ART) are often used interchangeably in literature.

***Auditory functioning:*** Functioning at the level of body or body part (World Health Organization, 2013, p.10), which for the current study encompasses hearing and auditory processing capacities.

***Auditory processing:*** Perceptual processing of auditory information in the central nervous system and the neurobiologic activity that underlies that processing and gives rise to electrophysiologic auditory potentials (American Speech-Language and Hearing Association, 2005a). For the purposes of this study, this definition contained in a technical report compiled by the American Speech-Language and Hearing Association (2005a) was used.

***Auditory processing capacities (skills):*** Discrete auditory processes such as localization, lateralization, temporal resolution (Canadian Interorganizational Steering Group for Speech-Language Pathology and Audiology, 2012, p.13), auditory discrimination, auditory pattern

recognition and auditory performance in competing acoustic signals (American Speech-Language and Hearing Association, 2005a). In line with the Canadian Interorganizational Steering Group for Speech-Language Pathology and Audiology (2012) guidelines, the term *auditory processing capacities* was used as it reflects the discrete processes that were assessed.

**CD4 count:** A laboratory test that measures the number of CD4 T lymphocytes (CD4 cells) in a sample of blood. In people with HIV, the CD4 count is the most important laboratory indicator of immune function and the strongest predictor of HIV progression (AIDSinfo, 2018, p.24).

**Fluid intelligence:** The innate learning capacity of an individual, not dependent on education or experience, which is used with relatively novel tasks, reasoning, and information analysis. Based on the Cattell-Horn theory of crystallized and fluid intelligence (American Psychological Association, 2019). Also considered to reflect nonverbal intelligence (McCallum, 2013).

**Highly active antiretroviral treatment (HAART):** See Antiretroviral Therapy.

**Hearing loss:** Reduction in hearing ability (Stach, 2010).

**Human Immunodeficiency Virus (HIV):** HIV is a virus that weakens the immune system, ultimately leading to AIDS (UNAIDS, 2015).

**Learning capacities:** For the purpose of the study, learning capacities refer to discrete cognitive processes that affect learning, including memory and intelligence (IQ) (Byrnes, 2012).

**Neurocognitive:** May affect executive function, motor skills and/or general intellectual functioning.

**Nonverbal intelligence:** See Fluid intelligence.

**Morbidity:** Disease state or symptom (AIDSinfo, 2018, p.113).

***Mortality:*** The state of being mortal (subject to death) (AIDSinfo, 2018, p.113).

***Opportunistic infection:*** An infection that occurs more frequently or is more severe in people with weakened immune systems, such as people with HIV or people receiving chemotherapy, than in people with healthy immune systems (AIDSinfo, 2018, p.126).

***Short-term memory:*** The ability to retain a small amount of information in a highly accessible state for a short time (Vergauwe & Cowan, 2014).

***T-helper cells:*** See CD4 count.

***Undetectable viral load:*** When the amount of HIV in the blood is too low to be detected with a viral load (HIV RNA) test (AIDSinfo, 2018, p.175).

***Viral load:*** The amount of HIV in a sample of blood (AIDSinfo, 2018, p.179).

***Viral suppression/virally suppressed:*** When antiretroviral therapy (ART) reduces a person's viral load (HIV RNA) to an undetectable level (AIDSinfo, 2018, p.180).

***Working memory:*** The small amount of information that can be held in an especially accessible state and used in cognitive tasks (Cowan, 2014).



## Chapter 1

### Introduction

#### Background

Research into the management of HIV in the last three decades has seen HIV become a chronic disease, and no longer a fatal one. The HIV landscape has changed from a situation where children typically died of AIDS to one where children are living with HIV. Research is now required to understand how children live with HIV as a chronic condition and how it affects their educational performance.

The importance of quality education has been highlighted by its inclusion as Sustainable Development Goal 4 (SDG 4) (United Nations, n.d.). Inclusive and quality education, particularly in low- and middle-income countries, is a priority as it is a crucial step towards escaping the poverty cycle (United Nations, n.d.). However, childhood hearing loss has been identified as a “significant barrier to achieving sustainable development goal 4” (LeClair & Saunders, 2019). Hearing loss in young children may lead to delays in cognition (Lederberg, Schick, & Spencer, 2013), as well as delays in speech and oral language development (Tye-Murray, 2009). Subsequently, communication skills, academic achievement, psychosocial behaviour and emotional development (Most, 2006) may be affected. In order to minimise the educational effects of hearing loss and achieve SDG 4, a better understanding of the burden of disease in South Africa is needed. This will enable health and education sectors to provide inclusive, quality services.

There is a growing body of literature focusing on hearing disorders in people living with HIV (PLHIV), as well as the changes that the disease may produce in the auditory system. Hearing loss, tinnitus and vertigo have all been reported (Khoza-Shangase, 2010; Maro et al., 2014; van der Westhuizen et al., 2013). However, the clinical manifestation of

these disorders in the auditory system may be due to a range of causes. This may include the disease itself, opportunistic infections associated with the disease, and ototoxicity, which may be due to the medication administered for the treatment of the opportunistic infections and/or ART being used to manage the disease (de Jong, Luder, & Gross, 2019; Ensink & Kuper, 2017).

### **Research Focus**

The increasing body of research in the field of hearing loss and HIV provides essential information regarding the disease process and its clinical impact on hearing. This body of research is primarily based on a bio-medical approach to the measurement of disease impact. The research reported in this dissertation is underpinned by concerns that it is essential to also understand the impact of living with chronic HIV and its manifestations on children, by considering their auditory functioning (hearing, as well as auditory processing capacities), and learning capacities (nonverbal intelligence (NVIQ), short-term memory (STM) and working memory (WM)).

### **Research Problem**

Currently, there is a paucity of research related to auditory manifestations of HIV in the paediatric population, particularly with how these relate to auditory functioning and the relationship to NVIQ, STM, and WM. A shortcoming in current research is the perspective that auditory functioning is limited to hearing loss. The idea of assessing hearing as a discrete physical entity does not consider that children with normal hearing may continue to experience difficulties in environments that require the child to process acoustic information, such as a classroom.

## Research Questions

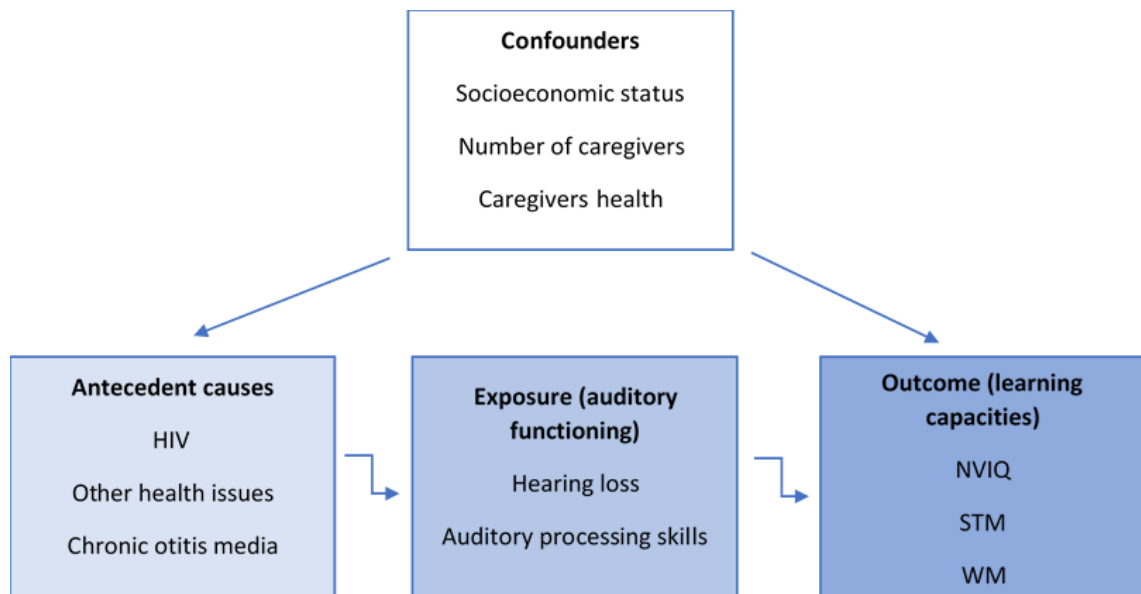
The study was underpinned by the following research questions:

1. Is there a difference in auditory functioning (hearing and auditory processing capacities) between CLHIV and CNLHIV?
2. Which predictor variables are associated with hearing loss in CLHIV?
3. Are there associations between auditory functioning, HIV status, and learning capacities (NVIQ, STM, and WM)?

## Epidemiological Framework

An epidemiological framework was established to facilitate consideration of the potential relationships between study elements and to consider the rationale for the inclusion of each study measure.

An *a priori* causal pathway was hypothesised that specified the most proximal Exposure and Outcome variables, the possible Antecedent causes to the Exposure, and the potential Confounders (Rothman, 2002). This pathway assisted in defining putative associations for testing. The proposed causal pathway is outlined in Figure 1. A summary of the components of the causal path is provided. These are discussed in more detail in Appendix D.



**Figure 1. Proposed Causal Pathway**

*Antecedent causes* are factors that are likely to be causally associated with the Exposure (Rothman, 2002). In this study, compromised auditory functioning (hearing loss and poor auditory processing skills/capacities) was the *Exposure* and HIV was proposed as an *Antecedent cause*. This proposal was based on research indicating that compromised auditory functioning was potentially a result of HIV and could be associated with the disease itself, the treatment for the disease, or with opportunistic infections (Assuiti et al., 2013; Maro et al., 2014). Furthermore, opportunistic infections were more likely to occur in CLHIV (Iroezindu, 2016), as well as chronic otitis media and conductive hearing loss (Smith et al., 2017).

*Outcome*, in this study, was learning capacities as measured by NVIQ, STM and WM. Compromised neurocognitive abilities have been observed in CLHIV with Sherr et al. (2018) reporting significantly lower scores for nonverbal cognitive ability. Musindo et al. (2018) did not only observe high occurrences of major neurocognitive disorders in the area of nonverbal intelligence, but also in the areas of planning ability and simultaneous processing. Poorer

executive function has also been reported in CLHIV (Ezeamama et al., 2016), with Cockcroft and Milligan (2019) and Sherr et al. (2018) observing difficulties with WM in CLHIV.

*Confounders* are variables that are associated with both Exposure and Outcome but are not proxies for Disease (Rothman, 2002). In this study, socioeconomic variables were proposed as a possible confounder. This confounder was included as the population under investigation not only had a disease (HIV) which may have affected the Exposure (auditory functioning) and Outcome (learning capacity), but typically came from socioeconomic backgrounds that have been associated with hearing loss (He et al., 2018), auditory processing difficulties (Tabone et al., 2017) and compromised learning (Maswikiti, 2008), even in the absence of HIV.

### **Placing the Researcher within the Research**

As an audiologist, my motivation for undertaking this study was to develop new knowledge about the way in which children with and without HIV, process auditory information and how this translates into a capacity to learn - as measured by NVIQ, STM, and WM. HIV is still a challenging disease in South Africa, despite widespread provision of HAART to children born with HIV. The use of HAART has been a significant factor in moving HIV from a fatal disease to a chronic one. However, it has long been suspected by audiologists and others working within the paediatric population, that ART may have subtle effects that have yet to be understood. The personal motivation for undertaking this research was to ensure that CLHIV have the same opportunities to learn, compared with their peers who are not living with the virus. Little is known about the impact of HIV on pre-teen children (9 - 12-year-olds) as most attention has been focussed on young children (5 years and younger), adolescents, and adults. There will be significant lifelong impacts if pre-teen children are unable to optimise their learning potential and capitalise on their learning

opportunities. South Africa needs a more employable next generation to reduce the current burden on its limited capacity to provide social welfare services (Hanass-Hancock & McKenzie, 2017). Retaining children in the schooling system for as long as possible is one way of ensuring their employability, particularly their capacity to continue to tertiary education and to earn a liveable wage (Statistics South Africa, 2019b).

The dissertation, as briefly described below, is presented as a compilation of two published papers and traditional chapters. The dissertation is divided into five main parts, which are further subdivided into chapters. Figure 2 provides an overview.

#### **Part 1:**

Chapter 1 provides the background to the study and presents the research problem, as well as the research questions. Furthermore, a summary of the epidemiological framework that was considered is provided.

Chapters 2 to 4 form the literature review. Chapter 2 provides an overview of HIV and presents the neurocognitive sequelae of HIV, which may influence learning. Chapters 3 and 4 are standalone papers. These papers systematically present the effects of HIV on hearing and auditory processing capacities.

#### **Part 2:**

Chapter 5 describes the study methodology. The aims and objectives are presented. The research design, as well as descriptions of the participants, procedures and measures used in this study, are provided. Statistical methods and analysis for each objective is included.

**Part 3:**

Chapter 6 reports the results of the study. The results as reported, reflect the four objectives of the study. Standalone papers reporting on these results are included as appendices (Appendices A-C).

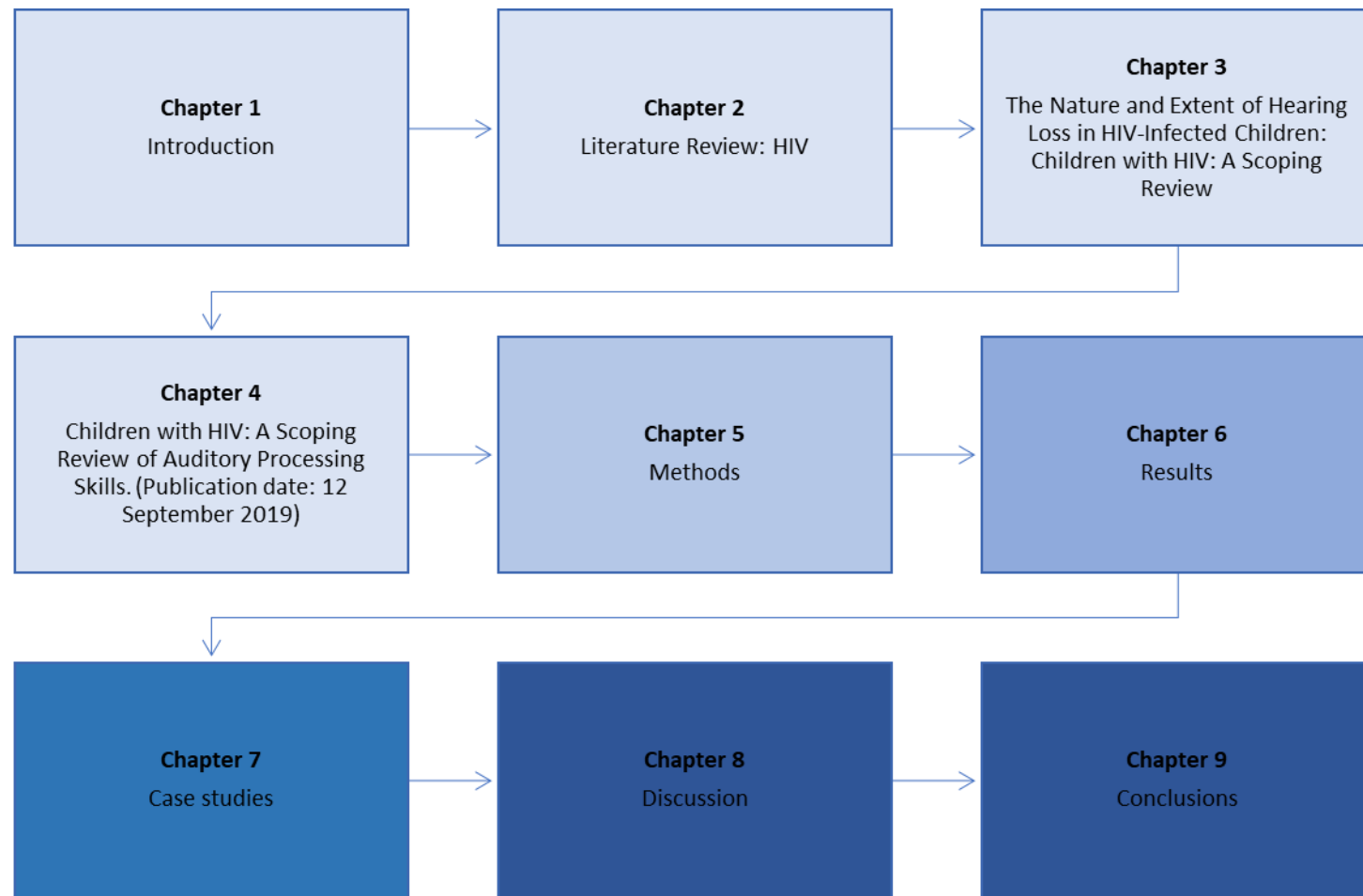
**Part 4:**

Chapter 7 is a standalone chapter presenting case-case and case-control dyads. The rationale for including this chapter is to provide insight into the complexities of having CLHIV in the classroom.

**Part 5:**

Chapter 8 provides a discussion of the results of the study. It begins by presenting the objectives and then continues by discussing these results relative to the stated objectives. Limitations of the study and clinical and research implications are presented.

Chapter 9 provides concluding comments.



**Figure 2.** *Overview of Dissertation*



## Chapter 2

### **Overview of HIV**

“AIDS today is not a death sentence. It can be treated as a chronic illness or a chronic disease.” (Yusuf Hamied, April 2004)

This chapter presents a brief history of HIV and discusses the challenges faced by children with HIV in the school system, focusing on some of the capacities involved in learning. The subsequent chapters discuss auditory functioning (hearing and auditory processing capacities) related to HIV. These chapters are reported separately as they are both systematic scoping reviews. Both reviews were best undertaken as scoping reviews to answer broad questions about what had been published on HIV and hearing loss, and HIV and auditory processing. A further aim in the scoping reviews was to describe how hearing loss and auditory processing had been measured in the literature.

### **A Brief History of HIV**

In 1983, HIV was identified as the cause of a terminal disease that had first been documented in 1981 (Melhuish & Lewthwaite, 2018; Whiteside, 2019). This disease was called acquired immunodeficiency syndrome (AIDS).

HIV is a retrovirus, more specifically, a lentivirus that continuously replicates, leading to the destruction of CD4 lymphocytes, which contribute to the immune system of the body. This slow-growing virus eventually destroys the CD4 lymphocytes, leaving the body susceptible to opportunistic infections and, if left untreated, eventually leads to AIDS (Melhuish & Lewthwaite, 2018). Initially, two types of viruses were identified, namely HIV1 from Central Africa and HIV2 from West Africa. However, the viruses were not contained and eventually spread throughout the world, reaching South Africa, the current epicentre of the HIV-epidemic, in the 1990s (Whiteside, 2019).

Despite treatment being available from 1996, most patients still died as the treatment was expensive, and there was restricted access thereto (Melhuish & Lewthwaite, 2018; Whiteside, 2019). However, 35 years later, effective ART has become readily available and more affordable, resulting in a near-normal life expectancy (Melhuish & Lewthwaite, 2018) with a 45% decrease in mortality since 2000 (UNAIDS, 2019).

Global estimates for 2018 reflect a total population of 37.9 million PLHIV, with 1.7 million being children younger than 15 years of age (World Health Organization, 2019). Although global statistics have shown a reduction of 33% in mortality and 16% in annual new infections when compared to 2010 figures, the virus continues to be omnipresent in Africa (World Health Organization, 2019).

Despite a recent decrease of 24% in new infections annually (compared to 2010), Africa continues to have the majority of PLHIV, namely 25.7 million (World Health Organization, 2019). The decline in the number of AIDS-related deaths (40% decrease in mortality relative to 2010) is evident in the increasing number of PLHIV (World Health Organization, 2019), and this can be attributed to the roll-out of ART. Estimated ART coverage in sub-Saharan Africa in 2018 was approximately 67% (AVERT, 2019a; Statistics South Africa, 2019a; World Health Organization, 2019).

Globally, as well as within the African region, South Africa continues to have the largest HIV epidemic, with estimates of PLHIV ranging from 13.5% (Statistics South Africa, 2019a) to 20.4% (AVERT, 2019b) of the total South African population. This equates to 7.7 million PLHIV, of which 260 000 are children under the age of 15 years (UNAIDS, 2018). South Africa also has the most extensive ART programme in the world, with 63% of adults and 64% of children being on Highly Active (HA) ART (AVERT, 2019b). Access to HAART has changed significantly since the early days of the virus and has increased the

lifespan of many South Africans (Statistics South Africa, 2019a). Despite the continued presence of HIV, life expectancy at birth is currently estimated at 61.5 years for males and 67.7 years for females (Statistics South Africa, 2019a), with implications for CLHIV, who are no longer impacted by issues of mortality, as much as morbidity.

### **HIV as a Chronic Illness**

The extensive rollout of ART in Southern Africa has changed the HIV landscape (Gates & Cysique, 2016) with HIV now being considered a chronic illness. Effective treatment, coupled with better treatment adherence, has led to better CD4 counts and viral loads, less opportunistic infections, and less HIV-related morbidity and mortality (Gates & Cysique, 2016).

However, chronic illness, by its very nature, is often associated with specific medical protocols such as aggressive treatment routines and multiple hospital appointments (Eiser, 1997), which may have an impact on an individual's everyday functioning. For many PLHIV, HAART has provided them with a better prognosis and improved life expectancy. However, the need for lifelong compliance, the possibility of long-term toxicity, and the complications of poor adherence are realities that PLHIV face, similar to persons living with other chronic health disorders (Lewthwaite & Wilkins, 2009).

Hence, the impact of living with HIV on quality of life and the capacity to engage fully with the community cannot be ignored. Research focusing on quality of life issues in CLHIV indicates that school functioning may be severely affected, with academic competence and performance being compromised (Bomba et al., 2010). Despite the efficacy of the medication, the research suggests that the availability of HAART does not necessarily improve psychosocial health (Bomba et al., 2010).

## **HIV in the Paediatric Population**

Approximately 1.3 million to 2.2 million children (aged 0 to 14 years) are living with HIV, with the majority calling sub-Saharan Africa their home (World Health Organization, 2019).

Most of these children acquired HIV via mother-to-child transmission (MTCT), where the virus was transmitted during pregnancy, childbirth, or breastfeeding (AVERT, 2018). Although the number of new infections has decreased due to the recent introduction of Prevention of Mother-to-Child Transmission (PMTCT) programmes (with an estimated 1.4 million infections among children being prevented over the period 2010 to 2018 (AVERT, 2018)), new HIV infections, particularly transferred via breastfeeding, are still occurring (AVERT, 2018; Le Roux et al, 2019). Despite these new infections (estimated at 160,000 [110,000 to 260,000] per year (World Health Organization, 2019)), CLHIV are living longer due to decreased mortality rates (Melhuish & Lewthwaite, 2018). This has significant implications for both health and education services.

## **HIV and Learning**

Advances in PMTCT programmes and HIV treatment have resulted in near normal life expectancy for these children (61.1 years for males and 67.3 years for females) (Statistics South Africa, 2019a). However, CLHIV are now faced with HIV-associated conditions that may affect their ability to function in their everyday environment, including their learning environment (Phillips et al., 2016).

One of the most prevalent conditions affecting PLHIV is HIV-associated neurocognitive disorders (HAND) (Farhadian, Patel, & Spudich, 2017). HAND encompasses various neurocognitive deficits that may include deficits in executive function (memory,

concentration, and attention), motor skills, and general intellectual functioning (intelligence) (Ezeamama et al., 2016; Farhadian et al., 2017; Hoare et al., 2016).

There is no clarity on how HIV causes these neurological complications. However, the central nervous system (CNS) may be affected in two ways, namely:

- by the virus itself (primary HIV CNS disease); or
- by an opportunistic infection as a result of a compromised immune system (secondary CNS disease) (Ellis, Calero & Stockin, 2009).

During acute infection, HIV enters the CNS via infected immune cells that cross the blood-brain barrier, causing CNS infection and immune activation (Farhadian et al., 2017). This CNS infection leads to the CNS macrophages releasing inflammatory cytokines and neurotoxins, resulting in damage to neurons, which in turn may cause primary HIV CNS disease (Ellis et al., 2009). Infants are particularly susceptible to neurologic complications as their blood-brain barrier is more permeable, and thus more vulnerable to damage caused by HIV (Moretti et al., 2015).

Hence, despite early initiation of ART, brain abnormalities indicating cerebral injury, has been observed in young CLHIV (Musielak & Fine, 2016). The neurologic consequences affecting these children include cerebrovascular disease, epilepsy, and cognitive impairment (Farhadian et al., 2017).

In their meta-analysis of 22 studies, Phillips et al. (2016) reported greater impairment in CLHIV for certain cognitive domains. They reported large effect sizes for working memory (ESE=16.46), processing speed (ESE=9.36), executive function (ESE=3.68), and visual memory (ESE=2.71). However, only statistically significant effects were found for executive function and processing speed. One interpretation for these findings may be that specific cognitive domains, rather than general intellectual functioning, are more severely

affected in CLHIV. However, the authors acknowledged that effect estimates might have reflected the heterogeneity in cognitive domains, as well as testing methods used (Phillips et al., 2016). Similar findings have been reported by other researchers (Ezeamama et al., 2016; Musindo et al., 2018; Cockcroft & Milligan, 2019), with Ezeamama et al. (2016) observing poorer executive function in CLHIV, despite the children receiving ART. Cockcroft and Milligan (2019) and Sherr et al. (2018) also reported on poorer executive functions in CLHIV, more specifically difficulties with working memory.

A high occurrence of major neurocognitive disorders, specifically in the areas of nonverbal intelligence, planning ability, and simultaneous processing was reported by Musindo et al. (2018). These findings were similar to those reported by Brahmabhatt et al. (2017), who observed that CLHIV presented with poorer scores for simultaneous processing, learning, and composite nonverbal cognitive performance measures than CNLHIV. Other researchers have also noted compromised intellectual functioning in CLHIV: According to James and Ittyerah (2016) and Patel et al. (2019), CLHIV had lower intelligence quotients (IQ), as measured by the WISC III, when compared to CNLHIV. Domains that were affected included verbal IQ, performance IQ, verbal comprehension index, and perceptual organization index (James & Ittyerah, 2016). It should be noted that the norms that were used to interpret the tests scores in this study were UK-based (James & Ittyerah, 2016) and US-based (Patel et al., 2019) even though the studies were conducted in India and Cambodia/Thailand respectively, where English is not the home language of the children. This may have impacted upon the results. The authors also postulated that the children's poor performance on tests of verbal ability reflected the environment in which they were growing up, as most of the children lived in care homes: Sherr et al (2017) proposed that poor cognitive skills in children who have been institutionalized, may be attributed to lack of

environmental stimulation. However, in contrast to James and Ittyerah's (2016) findings, Patel et al (2019) found that children who were living with their biologic parent(s), were more likely to present with lower scores on the Beery VMI Test of Visual-Motor Integration. Possible reasons for lower cognitive scores in these children may include lack of stimulation due to parental illness, or poverty (Harrison et al., 2017; Patel et al, 2019). On the other hand, positive predictors such as early initiation of ART (Patel et al., 2019), longer duration on ART (Brahmbhatt et al., 2017), as well as virologic suppression at a young age have been associated with better neurocognitive outcomes in school aged CLHIV (Crowell et al., 2015).

Considering that the research shows that CLHIV experienced higher occurrences of neurocognitive disorders, it is understandable that these children displayed educational difficulties (Musindo et al., 2018; Nkwata et al., 2017; Sherr et al., 2018) such as grade repetition, slow academic progression and higher rates of absenteeism (Anabwani, Karugaba, & Gabaitiri, 2016; Rukuni et al., 2018). Pufall et al. (2014), however, observed similar academic performances between Zimbabwean CLHIV and CNLHIV. Factors that they considered as having an adverse effect on academic performance, included socioeconomic factors (Pufall et al., 2014).

### **HIV and Socio-Economic Status**

The World Bank estimated that in 2011, 46.8% of the population of sub-Saharan Africa lived in poverty (World Bank, 2012). Not only is sub-Saharan Africa affected by poverty, but it is also home to the majority of PLHIV (World Health Organization, 2019). The impact of socioeconomic status on PLHIV is, therefore, relevant when considering the causal path for health conditions that have been attributed to the disease.

The association between HIV and poverty depends on the geographical location of the studies reporting on these constructs (Bunyasi & Coetzee, 2017; Steinert et al., 2017).

However, a relationship between HIV, AIDS, and poverty has been reported, with poor people experiencing more AIDS-related illnesses (Steinert et al., 2017), as well as a higher prevalence of HIV (Bunyasi & Coetzee, 2017). Existing studies attribute financial hardship caused by HIV, to increased expenses (as a result of hospital visits and treatment) and lower-income (as a result of missed workdays and limited employment opportunities) (Poudel, Newlands, & Simkhada, 2017; Punpanich, Gorbach, & Detels, 2012).

Socioeconomic status may have far-reaching consequences for CLHIV. According to Smith (2011), poorer children tend to perform more poorly at school due to their lack of access to good nutrition, proper housing, and adequate security. Furthermore, children from lower socio-economic groups typically attend schools that do not have adequate infrastructure and staff to optimise the learning process (Smith, 2011). In addition, the schooling of CLHIV may be negatively affected if they are required to care for ill parents or have been orphaned due to the disease (Pufall et al., 2014). Researchers, such as Pufall et al. (2014), thus suggests that other factors besides HIV be considered as possible contributors to poor educational outcomes, especially within the context of sub-Saharan Africa, where HIV, hearing loss, and poverty is prevalent.

This study focuses on auditory functioning (hearing and auditory processing capacities) and learning capacities as measured by NVIQ, STM and WM. This information will be used to increase awareness of the more subtle difficulties experienced by CLHIV, which in turn will guide interventionists and educators in planning suitable programmes for these children.



## Summary of Chapter 2

CLHIV currently have near-normal life expectancy due to HAART. However, HIV is now considered a chronic condition / disease, and may be associated with other co-morbid conditions. Although PMCTC programmes have been effective, new infections continue to occur in the paediatric population with half of these being ascribed to breastfeeding.

HIV crosses the blood-brain barrier through the immune cells, causing damage in the CNS with resultant neurocognitive impairments. Despite the early initiation of HAART, cognitive impairment continues to be observed in CLHIV. Deficits in executive function (including WM) and processing speed are evident. Academic consequences of HIV have also been noted, including higher absenteeism, grade repetition, and slow progress, while socio-economic factors may further impact on the effects of the virus.

Health and educational services will therefore need to consider the implications of HIV and its co-morbidities in children living with this disease. As Krishnakumar (2007, p. 40) succinctly states: “We believe it is as important to be able to say something about the capabilities as it is to say how we can enhance them and thus promote human development. It is not enough to be able to measure how much is achieved, but it is also essential to be able to say how things can be improved.”

## Chapter 3

### **HIV and Hearing Loss**

This chapter consists of a scoping review published in the International Journal of Pediatric Otorhinolaryngology (April 2020). The aim of the review was to explore the current body of evidence regarding the nature, extent, and associates of hearing loss in CLHIV. The review was undertaken to assist the primary investigator to set the scene for understanding what is known, and not known, about hearing loss in CLHIV. A secondary aim of the review was to explore current assessment measures used to measure hearing status.

This article was edited per the editorial specifications of the journal.

## **Abstract**

### **Introduction**

Antiretroviral therapy has had a major impact on life expectancy from HIV, as many people now live with it as a chronic disease. Chronic HIV has been associated with a range of comorbid disabilities and health conditions, one of which is hearing loss. Undiagnosed and untreated hearing loss, particularly in children, has been linked to poorer spoken language skills, with subsequent effects on academic performance.

### **Methods**

This systematic scoping review aimed to summarize the available peer-reviewed literature on hearing loss in HIV-infected children, specifically to describe its extent and nature. The review followed the framework proposed by Arksey and O'Malley. Key search terms included hearing loss (and synonyms), child (and synonyms), and HIV. Electronic databases (EBSCOhost Research Platform, PubMed, Web of Science and Scopus databases) were searched for any relevant articles published from 1 January 2000 to 30 June 2019. Reference lists of included articles were pearled for additional relevant articles not already identified. Each stage of the selection process was conducted independently by two authors. The results were then collated by a third author who also resolved any discrepancies. Extracted data included sample descriptors, audiologic tests, hearing loss prevalence, hearing loss descriptors, and factors associated with hearing loss.

### **Results**

Seventeen articles were included; 10 from Africa, four from South America, two from North America and the remaining article from Asia. Although most of the articles reported on pure tone audiometry, the samples as well as the cut-off criteria for normal hearing were

heterogenous. Prevalence of hearing loss varied across articles (from 6% to 84%).

Conductive hearing loss occurred more frequently than sensorineural or mixed hearing loss.

ART use and ear infection were reported as significant in three of five articles that reported on significant associates of HIV-related hearing loss.

### **Conclusion**

There was a modest volume of research from a limited number of countries. Heterogeneity in sampling and audiometric methods precluded a clear understanding of potential associations between chronic HIV-related hearing loss and contributing factors.

**Keywords:** HIV, hearing loss, auditory impairment, scoping review, pediatric

## Introduction

Effective treatment for HIV has resulted in a significant decrease in mortality rates over the last 10 years, with AIDS deaths globally for 2016 recorded at being 48% lower than the 1.9 million reported in 2005 [1]. This decrease has resulted in a subsequent increase in the number of people living with the disease, and in the life expectancies of these individuals. Since HIV is no longer one of the top ten global causes of death [2], the research agenda for HIV is changing from mortality to morbidity [3].

HIV is associated with conditions that can affect learning, including HIV-neurocognitive disorders [4,5] and hearing loss [6]. Hearing loss in young children in particular, may lead to delays in speech and spoken language development [7,8], and therefore can impact a child's communication skills, academic achievement, psychosocial behavior and emotional development [9,10]

Current literature reports on the prevalence of hearing disorders in both adults and children living with HIV, as well as the changes that the disease may produce in the auditory system. Studies have shown that adults who are infected with HIV may exhibit auditory and otologic disorders such as hearing loss, tinnitus and vertigo [11–15], with [15] reporting prevalence for tinnitus (26%), vertigo (25%), hearing loss (27.5%) and middle ear abnormalities (41%).

Studies, involving HIV-infected children, have also reported abnormal audiological findings, including otitis media and hearing loss [6,16,17], with hearing loss prevalence reportedly ranging from 4% to 85% with conductive hearing loss being more prevalent in children [6].

Although hearing loss, in this population, has been associated with various factors such as high viral load, the virus itself acting on the auditory system, ART and opportunistic

diseases; the evidence is not conclusive as hearing loss in HIV-infected individuals may be due to multiple factors [18]

*Aim:* This scoping review aimed to explore the current body of evidence regarding the nature, extent and associates of hearing loss in HIV-infected children. This information will afford relevant role-players (including parents, educators, medical professionals and governmental agencies), in both the education and health sectors, the opportunity to provide better services, by addressing the specific needs of HIV-infected children.

## **Methods**

*Protocol registration:* No protocol was registered for this scoping review.

*Choice of review methods:* A scoping review of the literature was considered to be the most suitable design for this study, which had the aim of summarizing the available evidence related to hearing loss in HIV-infected children [19,20].

*Reporting standard:* The Joanna Briggs Institute Reviewer's Manual, specifically Chapter 11 [21] and the PRISMA-ScR checklist [22] guided reporting. The scoping review was conducted according to the frameworks proposed by [20], and Levac et al. [19].

*Search timeframe:* The literature search was conducted from 1 January 2000 until 30 June 2019. The year 2000 was selected as it corresponded to the approximate period when the efficacy of HAART use in children and the subsequent decrease in mortality rates was determined [23].

*Eligibility criteria:* Table 1 summarizes the inclusion and exclusion criteria.

**Table 1. Inclusion and exclusion criteria**

<b>Inclusion</b>	<b>Exclusion</b>
HIV-infected children	Study participants were HIV infected adults
Articles reporting prevalence of hearing loss	Articles not reporting prevalence of hearing loss
Peer-reviewed journal articles	Non peer-reviewed journal articles, conference proceedings and any sources of grey literature
Research articles	Reviews, opinions and commentaries
Articles written in English	Articles not written in English

*Research question:* This review informed a larger subsequent study into the auditory skills of children with HIV/AIDS. The specific research question was “*What is currently known about hearing loss in HIV-infected children?*”.

*Identifying relevant studies:* A comprehensive search strategy (Table 2) was designed in collaboration with a university librarian. The literature search involved: EBSCOhost Research Platform (Medline, Africa Wide, Academic Search Primer and CINAHL), PubMed, Web of Science and Scopus databases. These databases were considered to be the ones that most commonly contained articles in the area of interest.

Table 2. Search strategy across databases

Database	Search/Mesh terms
EBSCOhost research	hearing loss or deafness or hearing impairment or deaf or hard of hearing AND children or adolescents or youth or child or teenager or teens or young people or kids or paediatric or pediatric AND HIV or human immunodeficiency virus or HIV/AIDS
Pubmed	hearing loss or deafness or hearing impairment or deaf or hard of hearing AND children or adolescents or youth or child or teenager or teens or young people or kids or paediatric or pediatric AND hiv or human immunodeficiency virus or hiv/aids
Web of Science	hearing loss or deafness or hearing impairment or deaf or hard of hearing AND children or adolescents or youth or child or teenager or teens or young people or kids or paediatric or pediatric AND hiv or human immunodeficiency virus or hiv/aids
Scopus	hearing loss or deafness or hearing impairment or deaf or hard of hearing AND children or adolescents or youth or child or teenager or teens or young people or kids or paediatric or pediatric AND hiv or human immunodeficiency virus or hiv/aids

The literature search was conducted by one author (E.O), with the assistance of a librarian

*Study selection:* The study selection procedure was based on the PRISMA process [24] as depicted in Figure 1. Each step was independently completed by two authors (H.E. & E.O.) and the results were then collated by a third author (G.D.). All discrepancies were noted and returned to H.E. and E.O. for discussion. If these authors could not resolve the discrepancy, G.D. was consulted for a final decision

*Charting the data:* Data extraction sheets (Tables 3 – 5), as recommended by [19,20,25], were used to extract and summarize the relevant data. Information was extracted on author(s), year, city and country, study design, sample size, sample age, research design,

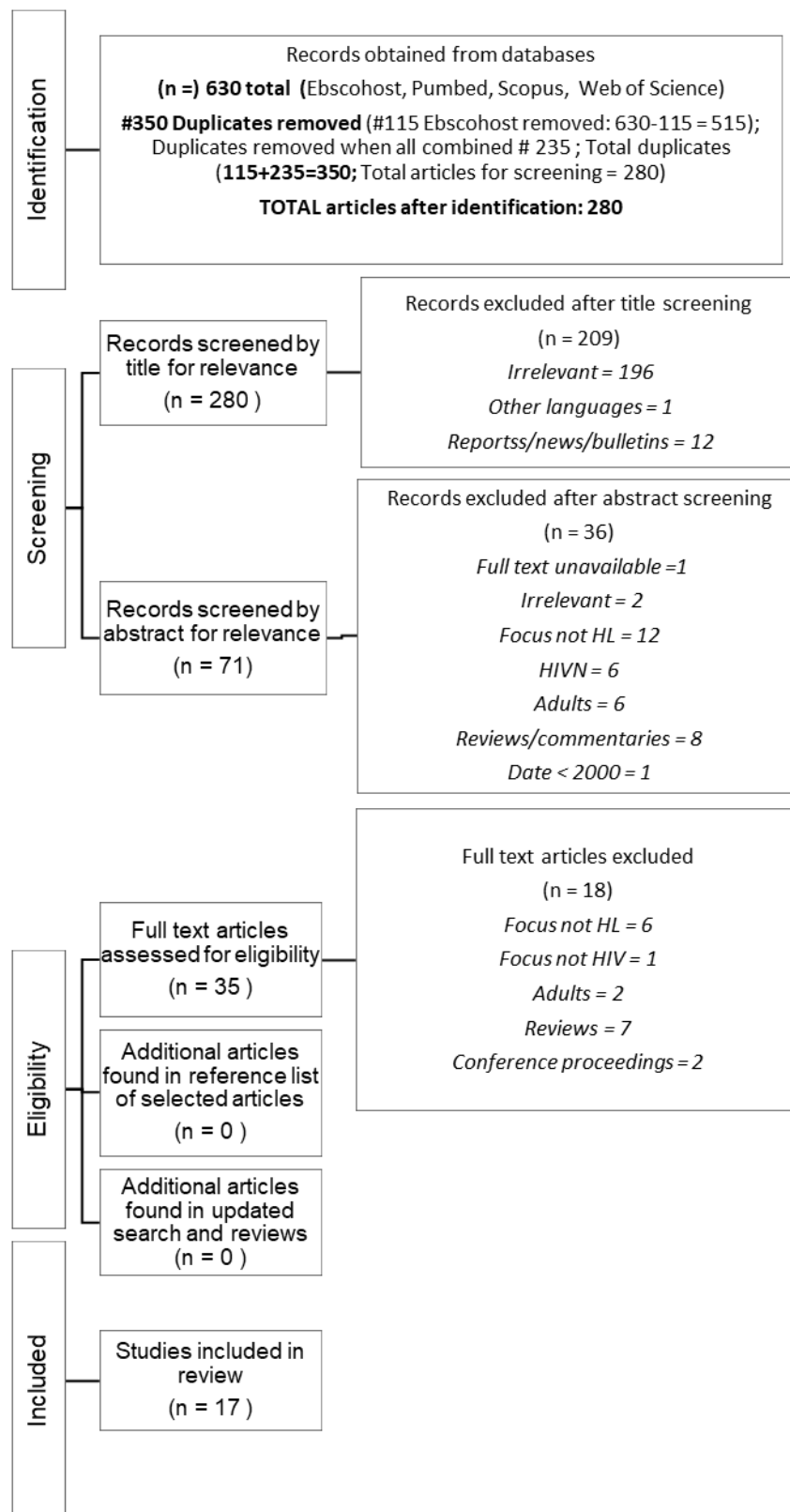


audiologic tests, prevalence of hearing loss and nature of hearing, factors associated with hearing loss.

*Collating, summarizing and reporting the results:* Tables, figures and numerical analysis, as recommended by [20], were used to report the results.

## **Results**

*Study Selection:* Figure 1 outlines the study selection process. Of the initial 630 articles, 280 remained after duplicates were removed. The titles of these articles were screened for relevance, resulting in 209 articles being excluded. The abstracts of the remaining 71 articles were then screened for relevance. Thirty-five articles were included for full text review of which 18 were excluded as not meeting inclusion and exclusion criteria (Table 1). The remaining 17 articles were considered to be relevant to the research question [16,17,26–40]. No additional articles were found during pearling.



**Figure 1:** Flowchart depicting selection of articles

*Study characteristics:* The studies were all cross-sectional observational designs and included a total of 2617 children (study samples ranging from 23 to 380 children). Two studies [26,30] reported on the same sample, therefore, their sample numbers were only included once in the calculation of total subject numbers. The ages of the children ranged from three months to 20 years. Although the exclusion criteria for age was 18 years, two studies were included despite the age ranges of the study participants being four to 19 years [41] and seven to 20 years [16]. Not all studies reported mean ages, thus it was not possible to estimate average age of the participants. Based the available data, it was postulated that most of the children were younger than 12 years. The two studies that included 19 and 20 year olds, reported mean ages of nine years, nine months [41] and 13 years, six month [16] respectively. Thus, it was assumed that the majority of participants in these two studies were within the inclusion criteria of 18 years (Table 3). A second study included adults [30], however, data were reported separately for children and adults and the elements required for the review could be extracted for children.

Eight studies were surveys which did not include control groups [17,27,28,31,32,34,35,37], while nine were case-control studies, with the controls being uninfected children [16,26,29,30,33,36,38–40]. The studies were all conducted in urban settings; with 10 studies based in Africa, four in South America two in North America and the remaining study in Asia. Table 3 summarizes the reference populations of the included studies.

Table 3. Demographic information of each study

Author(s), year	Study setting	Study design	Cases (n)	Controls (n)	Age range, (years / years:months)
Matas et al. 2006	São Paulo, Brazil	Case control	51	50	3 to 10
Palacios et al. 2008	Mexico City, Mexico	Survey	23	-	0:05 to 17 (median = 4:06)
Khoza-Shangase & Turnball 2009	Johannesburg, South Africa	Survey	62	-	1:06 to 6
Matas et al. 2010	São Paulo, Brazil	Case control	51	50	3 to 10
Govender et al. 2011	Cape Town, South Africa	Survey	78	-	0:03 to 12 (mean = 5:03)
Taipale et al. 2011	Luanda, Angola	Case Control	78	78	0:09 to 14:08 (median = 4:03 HIVP; 4:02 HIVN)
Chao et al. 2012	Lima, Peru	Survey	139	-	4 to 19 (mean = 9:09)
Makar et al. 2012	Kolkata, India	Survey	67	-	4 to 16 (mean = 11:06)
Torre et al. 2012	Various sites, USA	Case control	145	86 (HEU)	7 to 17 (mean = 12:02)
Buriti et al. 2013	João Pessoa (Paraíba), Brazil	Survey	23	-	2 to 10:11 (mean = 5:07)
Christopher et al. 2013	Mulago (Kampala), Uganda	Survey	370	-	0:06 to 5 (mean = 3:02)
Devendra et al. 2013	Lilongwe, Malawi	Case control	296	296	2 to 9 (mean = 5:06 HIVP; 6:01 HIVN)
Torre et al. 2015	Cape Town, South Africa	Case control	37	24	4-14 (mean = 7.01)
Hrapcak et al. 2016	Lilongwe, Malawi	Survey	380	-	4 to 14 (mean = 8:06)
Maro et al. 2016	Dar es Salaam, Tanzania	Case control	131	113	0:8 to 18 (mean = 10:01 HIVP; 10.01 HIVN)
Nakku et al. 2017	Mbarara, Uganda	Case control	148	79	6 to 12 (mean = 9.2)
Smith et al. 2017	Addis Ababa, Ethiopia	Case control	107	147	7 to 20 (mean = 13:06 HIVP; 13 HIVU)

HIVP = HIV positive; HEU = HIV exposed and uninfected; HIVN = HIV negative; HIVU =

HIV status unknown

*Synthesis of the results*

The 17 articles reported on 16 datasets. Not only did the study samples differ in age, but they also differed in selection criteria and health status. Although all articles reported on the sampling location, information on how children were selected for study participation was generally absent. Overall, the included papers reported on 1940 HIVP children (cases) and 677 uninfected children (controls). The uninfected children included children who were exposed to HIV, but not affected, as well as children who were reported to be uninfected despite not being tested. Not all the HIVP children were receiving antiretroviral therapy.

**Table 4:** Key characteristics of included articles as these relate to extent of hearing loss

Author(s), year	Audiologic assessment measure (hearing loss cut-off)	Prevalence of hearing loss in HIVP children	Prevalence of hearing loss in Controls	Significant findings related to prevalence
Matas et al. 2006	Otoscopy, PT (>15 dB), neurologic ABR, tympanometry and acoustic reflexes	37% (19/51)	0% (0/50)	Significant difference in hearing loss prevalence between cases and controls
Palacios et al. 2008	Otoscopy, PT (>20dB), ABR (>20dB), speech discrimination	33% (4/12) – PTA 23% (6/23) – ABR	-	Not applicable
Khoza-Shangase & Turnbull 2009	Otoscopy, tympanometry, screening protocol for DPOAE and TEOAE (refer)	32% (20/62)	-	Not applicable
Matas et al. 2010	Otoscopy, PT (>15dB), neurologic ABR, tympanometry and acoustic reflexes, speech audiometry	28% (14/51)	0% (0/50)	Not applicable as comparison between children and adults
Govender et al. 2011	Clinical suspicion of hearing loss	6% (5/78) (confirmed with ABR)	-	Not applicable
Taipale et al. 2011	Otoscopy, PT (>25dB), ABR (>40dB)	26% (20/78)	15% (12/78)	Cases significantly more likely to have bilateral hearing loss than controls
Chao et al. 2012	Otoscopy, PT (>25dB), tympanometry	39% (54/139)	-	Not applicable
Makar et al. 2012	Otoscopy, PT (unspecified), tympanometry and acoustic reflexes, speech recognition threshold	33% (22/67)	-	Not applicable

Torre et al. 2012	PT ( $\geq 20$ dB), tympanometry	20% (29/145)	10% (9/86)	Mean pure tone average in worse ear significantly higher in cases than in controls
Buriti et al. 2013	Otoscopy, PT(>15dB), tympanometry and acoustic reflexes	84% (39/46 ears)	-	Not applicable
Christopher et al. 2013	Otoscopy, ABR (>25dB), tympanometry	33% (121/370)	-	Not applicable
Devendra et al. 2013	WHO TQS, Follow up Questionnaire	12% (36/296)	2% (7/296)	Odds of hearing loss significantly higher in cases than controls
Torre et al. 2015	Otoscopy, PT (>15dB), DPOAE, tympanometry	21% (8/37)	8.3% (2/24)	Mean pure tone average in worse ear significantly higher in cases than in controls
Hrapcak et al. 2016	Otoscopy, PT (>20dB), TEOAE, tympanometry	24% (90/380)	-	Not applicable
Maro et al. 2016	PT (>25dB), ABR, DPOAE, tympanometry, gap detection	17% (16/97)	6% (5/80)	Cases had a significantly higher proportion of pure tone averages greater than 25dB than controls
Nakku et al. 2017	Otoscopy, PT (not specified)	22%* (33/148)	23%* (18/79)	None
Smith et al. 2017	Otoscopy, PT (>25dBHL)	38% (41/107)	12% (18/147)	Significantly more cases than controls presented with hearing loss  Conductive loss occurred significantly more in cases than on controls

\*Values calculated from Figure 1 in article (Nakku et al. 2017)

***Audiologic assessment measures:*** As reported in Table 4, the assessment measures primarily comprised routine audiologic tests which included: otoscopy, pure tone audiometry (PT), tympanometry, auditory brainstem response testing (ABR), distortion product (DPOAE) and transient evoked (TEOAE) otoacoustic emissions. All but one study [32] specified which tests were used. The majority of studies used PT as the measure of hearing sensitivity [16,17,26–30,35–37,39–42]. Only Christopher et al. [28] used ABR to determine hearing status. The cut-off points for normal hearing was 15dBHL in four studies [26,30,37,43] , 20dBHL in three studies [17,27,36], 25dBHL in five studies [16,28,33,39,41] and 40dBHL (for ABR) in one study [33]. Two studies did not specify cut-off criteria [35,40].

Two studies did not include tests of hearing sensitivity. One used otoacoustic emissions as a screening measure [31] and the other used the WHO Ten Question Screen (WHO TQS) and a follow-up questionnaire [38].

***Extent of hearing loss:*** Among the HIVP children, the prevalence of hearing loss ranged from 6% to 84% (Table 4). The four studies that categorised hearing loss as a pure tone average greater than 15dB, reported prevalence rates between 22% and 84%. The studies that had a pure tone average of greater than 20dB as the criteria for diagnosing a hearing loss, reported prevalence ranging from 16% to 39%. Three studies reported a significant difference in the prevalence of hearing loss between cases and controls [16,26,38]. However, all case-control studies consistently reported a greater prevalence of hearing loss in HIV-infected children compared to the uninfected population.



**Table 5:** Key characteristics of included articles as these relate to nature of hearing loss in HIVP children

<b>Author(s), year</b>	<b>Symmetry</b>	<b>Type of hearing loss</b>	<b>Degree of HL</b>	<b>Significant HIV-factors associated with HL</b>
Matas et al. 2006	Not specified	Peripheral HL = 58%  Auditory brainstem disorders = 18%  Combination HL = 26%	Not specified	Not a study objective
Palacios et al. 2008	Bilateral = 33% (2/6)  Unilateral = 67% (4/6)	Auditory brainstem results:  Conductive = 75% (6/8 ears)  Sensorineural = 25% (2/8 ears)	Mild = 25% (2/8 ears)  Moderate = 75% (6/8 ears)	Findings not significant
Khoza-Shangase & Turnbull 2009	Bilateral = 65% (13/20)  Unilateral = 35% (7/20)	Conductive = 90% (18/20)  Sensorineural = 10% (2/20)	Not applicable	Inferential statistics not reported
Matas et al. 2010	Not specified	Conductive = 93% (13/14)  Sensorineural = 7% (1/14)	Not specified	Not a study objective
Govender et al. 2011	Not specified	Sensorineural = 100%	Not specified	Not a study objective

Taipale, et al. 2011	Bilateral = 50% (10/20) Unilateral = 50% (10/20) N - extrapolated	Not specified	Moderate hearing loss or greater = 25% (5/20)	Not a study objective
Chao et al. 2012	Bilateral = 52% (28/54) Unilateral = 48% (26/54)	Conductive = 89% (48/54) Sensorineural = 2% (1/54) Mixed = 9% (5/54)	Mild = 54% Moderate = 7% Moderate-severe = 4% Severe = 1%	CD4 count $\leq$ 500cells/ml) * (OR 3.53(1.21-22.4)) Undetectable viral load* (OR 4.33(1.58-11.9)) TM perforation* (OR 7.08(1.65-30.5)) Abnormal tympanometry* (OR 2.71(1.09-6.75)) *Adjusted OR
Makar et al. 2012	Not specified	Conductive = 45% (10/22) Sensorineural = 55% (12/22)	Not specified	Not study objective
Torre et al. 2012	Bilateral = 48% (14/29) Unilateral = 52% (15/29)	Conductive = 38% (11/29) Sensorineural = 62% (18/29)	Not specified	CDC class C (OR 2.81(1.22-6.48))
Buriti et al., 2013	Not specified	Not specified	Not specified	Opportunistic disease (otitis) (p<0.05) ART (p<0.05)

Christopher, et al. 2013	Not specified	Conductive = 36% (44/121) Sensorineural = 64% (77/121)	Mild = 36% Moderate = 58% Severe = 6%	Not a study objective
Devendra et al. 2013	Not specified	Not specified	Not specified	Not a study objective
Torre et al. 2015	Bilateral = 25% (2/8) Unilateral = 75% (6/8)	Conductive = 62.5% (5/8) Sensorineural = 37.5% (3/8)	Not specified	Findings not significant
Hrapcak et al. 2016	Bilateral = 40% (36/90) Unilateral = 60% (54/90)	Conductive = 82% (103/126 ears) Sensorineural = 14% (17/126 ears) Mixed = 4% (6/126 ears)	Mild = 66.7% (84/126 ears) Moderate = 20.6% (26/126 ears) Severe = 7.1% (9/126 ears) Profound = 5.6% (7/126 ears)	Frequent ear infection (OR 7.4(4.2-13.0)) Ear drainage (OR 6.4(3.6-11.6)) WHO stage 3 (OR 2.1(1.2-4.5)) WHO stage 4 (OR 6.4(2.7-15.20))
Maro et al. 2016	Not specified	Not specified	Only better ear results reported	Findings not significant

Nakku et al. 2017	Not specified	Conductive = 64% (21/33)	Not specified	Increasing age of child (p=0.01)
		Sensorineural = 33 % (11/33)		History of ear infection (p<0.01)
		Mixed = 3% (1/33)		Tuberculosis treatment (P<0.01)
				More than 6 years on ART (p<0.01)
Smith et al. 2017	Not specified	Conductive = 59% (24/41)	Not specified	Inferential statistics not reported
		Sensorineural = 24% (10/41)		
		Mixed = 17% (7/41)		
Peripheral hearing loss affects the peripheral auditory system and refers to conductive, sensorineural or mixed hearing loss				

**Nature of hearing loss:** Table 5 summarizes key findings of the studies, relating to the nature of hearing loss reported in the HIV-infected children.

Seven of the 17 articles reported on laterality. The majority of articles (four) reported a higher occurrence of unilateral hearing loss [17,27,36,44]. Of the remaining three articles, two found that bilateral hearing loss occurred more often than unilateral hearing loss [31,45], while one reported an equal amount of unilateral and bilateral hearing loss [33].

Of the 13 articles describing type of hearing loss, one article [26] categorised hearing loss as peripheral hearing loss, auditory brainstem disorders and mixed (peripheral + auditory brainstem disorders), one article only reported on sensorineural hearing loss [32] while all the other articles referred to conductive, sensorineural and mixed (conductive + sensorineural) hearing loss. Of the 11 articles that used the latter description for type of hearing loss, the majority (eight) reported that conductive hearing loss occurred more often than sensorineural (three) and mixed hearing loss (zero) [16,17,27,30,31,40,44,45].

Degree of hearing loss was described in six articles [17,27,28,33,39,45]. However, as one of the articles reported findings for the better ear only [39], it was excluded for further analysis.

Of the five remaining studies, three reported that mild hearing loss occurred most often [17,33,45], while the remaining two reported that moderate hearing loss occurred most often.

Of the 12 articles that reported on HIV-related factors associated with hearing loss; four did not include inferential statistics [16,28,31,42]. Of the remaining studies, three did not report significant associations [27,39,44]. Three found a significant association between hearing loss and current or previous ear infection [17,37,40] and three studies reported a significant association between hearing loss and antiretroviral therapy [37,40,41]. Furthermore, two studies found a significant association between hearing loss and stage of disease [17,46].

Nakku et al. [40] also reported significant associations between hearing loss and increasing age of child, as well as with comorbid tuberculosis treatment.

## Discussion

This is the first systematic scoping review that we know of, that focusses exclusively on the extent and nature of hearing loss in HIV-infected children. Our search strategy (including pearling as a validation step) was sufficiently comprehensive to enable identification of the available relevant literature [17] pertaining to our research question. We were surprised at the number of studies that have been published on this topic. Overall in these studies, approximately 1:3 HIV-infected children had some form of hearing loss. This prevalence is higher than the pooled prevalence estimates (13.1%) reported in a review of 88 papers by Wang et al. [47]. The review included papers reporting on hearing loss in healthy children (aged 0 to 18 years), who were not at risk of having a disease associated with hearing loss. Only papers that reported on, were included. This difference in prevalence may be because Wang et al. [47] used bilateral hearing for the calculation of prevalence whereas the studies included in this review used both unilateral and bilateral hearing loss to determine prevalence. Prevalence varied considerably across studies. A similar finding was reported by Ensink et al. [6] in their systematic review of 21 studies on hearing loss in HIV-infected children and adults. The review included 12 studies related to children of which 11 are included in our review. A possible reason for this variation was methodological differences in assessment measures, assessment environments and cut-off criteria used for determining normal hearing [47,48].

Conductive hearing loss occurred more frequently in HIV-infected children than either sensorineural hearing loss or mixed hearing loss. However, this finding is not specific to HIV-infected children as conductive hearing loss has been reported to account for more than 80% of all hearing loss in the general paediatric population [49,50].

Unilateral hearing loss seems to be more prevalent in HIV-infected children than bilateral hearing loss. Higher occurrence of unilateral hearing loss caused by chronic suppurative otitis media has also been reported in a population based study in rural Malawi [51]. Although this study did not specifically look at the HIV-infected population, the similarities between the findings of our review and the study by Hunt et al. [51] may in part be due to other factors, associated with conductive hearing loss (such as passive smoking, allergies, nursery attendance, being the third or later sibling and poor nutrition) that may be similar [50].

Although there was limited data on the degree of hearing loss, the most frequently occurring categories were “mild” and “moderate” hearing loss. Given that conductive hearing loss, probably due to opportunistic ear infection, was the most commonly occurring hearing loss, these categories correlate as mild to moderate hearing loss is associated with otitis media with effusion [52]. ART, especially HAART, has been reported to reduce the incidence of opportunistic diseases, however it has been found that the reduction of opportunistic disease due to HAART use is less pronounced in low to middle income countries where other factors (e.g. poverty and poor living conditions) may have an impact on the health status of the individual [53].

ART, stage of disease and current or past ear infection appears to be prominent factors associated with HIV. A higher WHO or CDC stage reflects that the individual is immune compromised which places them at risk of opportunistic disease such as ear infections. As the disease progresses it may affect various body systems which could lead to disability, including hearing loss [54]

*Limitations:* The review used a comprehensive search strategy to identify as much relevant literature as possible, and it highlights the scarcity of research on hearing loss in HIV-infected children. We were concerned that the inclusion of only English language studies may

have introduced bias toward countries from the Global North, however, we were surprised that only one study was based in this region and that the remaining studies were all based in the Global South. Although the exclusion of conference abstracts and other grey literature may have introduced publication bias; including this type of literature may not have provided sufficient detail for the purposes of this review.

## **Conclusion**

The evidence suggests an association between pediatric chronic HIV and hearing loss, that is predominantly conductive in nature. Although hearing loss prevalence is greater in HIV-infected children than in the general pediatric population, It is difficult to determine the extent as hearing loss prevalence varies relative to the hearing test and cut-off criteria used. There seems to be associates of hearing loss in HIV-infected children, however, the association between these variables and hearing loss is inconclusive.

In order to improve the health and education services offered to HIV-infected children, a better understanding of the impact of the virus and subsequent treatment is needed. Carefully designed case control studies looking at the time-sequence and relationship between HIV, HIV-related variables and hearing loss in children should be considered. Furthermore, research needs to address issues of testing methodology, sampling rigour, sample size calculation, and sample heterogeneity, as well as exerting better controls for age as this may be a confounding variable for opportunistic infections such as otitis media.



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## Reflections on Findings

The findings from the scoping review suggest that there is an association between paediatric HIV and hearing loss, that is predominantly conductive in nature. It appears that hearing loss prevalence is greater in CLHIV, than in the general paediatric population. However, it is difficult to determine the strength of the association or the extent of the differences between CLHIV and CNLHIV from this review, as there are several factors which should be considered.

From the review, it is postulated that the probable cause for the higher occurrence of conductive hearing loss in CLHIV is middle ear infection due to a compromised immune system. However, Midgley et al. (2000) and Marriage, Brown and Austin (2017) have reported that age, as well as seasonal changes, is also associated with otitis media.

Otitis media is common in young children, with more than 80% of four-year olds having had an episode of otitis media during their lifetime (Marriage et al., 2017). Considering that fourteen of the studies included in the review had children younger than six years old, age should be considered as a confounder. This has implications for the interpretation of the results and unless the study samples are stratified according to age, the association between HIV and conductive hearing loss remains inconclusive.

Prevalence rates for otitis media fluctuate relative to the season, with higher rates typically noted during the winter months (Marriage et al., 2017). The studies included in the review did not report on when the hearing assessments took place. Thus, the impact of seasonal fluctuation on the prevalence of otitis media in CLHIV cannot be determined.

In addition, the studies did not report on demographic and socio-economic factors that may have confounded the results. These factors include day care attendance, exposure to passive smoking, allergies and socio-economic status (Hunt et al., 2017; Marriage et al., 2017; Midgley et al., 2000).



Another important variable to consider when reviewing the literature is measures used to assess auditory functioning. The findings from the review highlight the need for the use of comparable testing methodologies. Most studies used pure tone audiometry to measure hearing status, with reported cut-off criteria for normal hearing ranging from 15dB to 25dB. The studies using lower cut-off criteria did not necessarily report higher prevalence rates, as would be expected with a more stringent cut-off. However, a possible reason for the varying rates may be the environment in which testing took place.

A further consideration is the inherent limitations of the audiological test used. The results obtained via conventional behavioural audiometry may not be accurate in “difficult-to-test” or younger children as the test relies on executive functions such as attention. Children may habituate to the sound and fail to respond, or consistent responses may only be observed at levels that are above threshold (Jerger & Hayes, 1976). Age and executive function are, therefore, important factors to consider when selecting suitable tests, especially when considering that neurocognitive deficits have been reported in CLHIV (Phillips et al., 2016).

A few studies used auditory brainstem response testing, particularly for younger children. Although this test is considered to be objective, interpreting the results involves subjectivity. According to Gans (1987), ABR testing results should be interpreted with caution in children who have neurologic involvement. This implies that when interpreting the ABR testing results of CLHIV, cognisance should be taken of the possible effects of the well-documented neurocognitive deficits (Phillips et al., 2016) in this population.

In order to improve the health and education services offered to HIV-infected children, a better understanding of the impact of the virus and subsequent treatment is needed. The current evidence regarding the association between HIV and hearing loss is not conclusive due to the presence of confounders related to the heterogeneity of the samples, as

well as the testing methodologies. Carefully designed case control studies examining the time-sequence and relationship between HIV, HIV-related variables and hearing loss in children, should be considered. Furthermore, research needs to address issues related to assessment methods, cut-off criteria, sampling rigour, sample size calculation, and sample heterogeneity.

## Chapter 4

### **HIV and Auditory Processing**

This chapter consists of a scoping review published in PLOS ONE (September 2019). The aim of the review was to explore the current body of evidence regarding the nature of auditory processing capacities in CLHIV. The review was undertaken to assist the primary investigator to set the scene for understanding what is known, and not known, about auditory processing in CLHIV. A secondary aim of the review was to explore current assessment measures used to measure auditory processing capacities.

This article was edited per the editorial specifications of the journal.

## **Abstract**

### **Introduction**

Auditory processing disorders can negatively affect academic performance in children. They can result from a number of aetiologies, including the human immunodeficiency virus (HIV). Although studies in paediatrics are limited, research suggests that HIV-infected children display poorer auditory processing skills than uninfected children.

### **Methods**

The aims of this study were to scan the peer-reviewed literature on auditory processing skills in HIV-infected children, to describe how auditory processing was tested, how auditory processing skills were reported, and to identify gaps in current evidence. This systematic scoping review was conducted using a modified version of Arksey and O'Malley's framework. Key words comprised 'HIV', 'auditory processing', 'hearing' and 'child'.

Electronic databases were searched for relevant articles published from 1 January 2000 to 30 April 2018, and reference lists of included studies were pearled. Two researchers reviewed the articles and extracted data on sample descriptors, auditory processing testing procedures, and auditory processing skills. A third author collated the results and resolved discrepancies. The American Speech-Language-Hearing Association description of auditory processing skills framed the analysis.

### **Results**

Five articles were included in this review (three from Brazil, one each from Mexico and Tanzania). Samples, and methods of testing were heterogeneous. Three studies reported on localization abilities, while gap detection thresholds, performance on dichotic tasks and speech discrimination scores were reported in one article each. No one study tested all areas of auditory processing skills and there was limited information about the auditory processing skills required for learning.

## **Conclusion**

This review highlighted the current sparse evidence-base for auditory processing in HIV-infected children. It identified the need to standardise testing procedures, measures of auditory processing skills, and sample selection.

## Introduction

Effective drug regimens have resulted in decreasing mortality rates from the human immunodeficiency virus (HIV) [1]. This has shifted attention to the impact of HIV on the developmental and educational outcomes of the approximately 1.8 million children, who are currently living with HIV [2]. HIV-infected children have been shown to perform poorer academically than their non-infected peers, with 40% of infected children aged between six and 12 years, being in a lower grade than is appropriate for their age [3]. It has therefore been suggested that HIV-infected children be recognised as a group with distinct educational needs [4]. However, in order to address their specific educational needs, research is required to describe the associated conditions affecting educational achievement.

Research has shown an association between hearing loss and HIV in the paediatric population with prevalence rates ranging from 6% to 84.4% [3,5–13]. Hearing loss in this population may be caused by the virus itself, opportunistic diseases and associated treatment regimens [14]. Hearing loss, which leads to reduced access to auditory information, significantly impacts a child's ability to listen and learn in a mainstream classroom environment [15]. However, listening difficulties may not only be associated with hearing loss but more subtly, a child can have normal hearing but an impaired ability to process auditory information [16].

Auditory processing can be described as assigning meaning to what has been heard [17]. Discreet auditory processing skills form the foundation for listening [18]. These skills include: sound localization and lateralization, auditory discrimination, auditory temporal processing, auditory pattern processing, dichotic listening, auditory performance in competing acoustic signals, and auditory performance with degraded acoustic signals [19]. Whilst there is disagreement in the international literature about how or where auditory

processing difficulties originate, for children with these deficits, the ability to function in a typical class environment is diminished [20].

Overall, research within HIV-infected populations has primarily reported on peripheral hearing loss [21], with few studies reporting on auditory processing. Although findings suggestive of central auditory deficits have been reported [5,8,22,23], these studies looked at the integrity of the auditory pathway rather than specific auditory processing skills. Matas et al [24], however, found that HIV-infected children were poorer at localizing sound than uninfected children. These findings have important implications for the paediatric HIV population, as disorders affecting auditory processing, in the absence of hearing loss, have been associated with poorer educational outcomes [25].

## **Objective**

The aim of this review was to systematically scan the published literature to identify papers of any research design that reported on auditory processing skills in the HIV-infected paediatric population.

## **Methods**

### **Study design**

A scoping review entails mapping key concepts and summarising available evidence of a particular research area [26,27]. A scoping review was the most appropriate design to address the objectives of this study, because so little is known about this area [28].

### **Protocol registration**

No protocol was registered for this scoping review as it was part of a bigger study that required the protocol to be registered by the Health Research Ethics Committee, Stellenbosch University.

## **Reporting standard**

This paper uses the PRISMA-ScR checklist [29] as a reporting standard. The review was conducted according to the framework proposed by Arksey and O'Malley [26], which was further developed by Levac, Colquhoun and O'Brien [27].

## **Eligibility criteria**

The search was conducted from 1 January 2000 until 30 April 2018. A PIO search framework was set, where P (patient) reflected children up to 18 years with HIV, I (intervention) was the assessment measure(s) for auditory processing skill(s), and O (outcome) was the auditory processing skill. Studies that included both adults and children were excluded. The inclusion and exclusion criteria are provided in Table 1.



**Table 1:** Inclusion and exclusion criteria

<b>Inclusion</b>	<b>Exclusion</b>
Article reported on a specific auditory processing skill; namely sound localization and lateralization, auditory discrimination, auditory temporal processing, auditory pattern processing, dichotic listening, auditory performance in competing acoustic signals, and auditory performance with degraded acoustic signals [19]	Article did not refer to a specific auditory processing skill
Peer-reviewed journal articles	Non peer-reviewed journal articles, conference presentations and other sources of grey literature
Research/data driven articles only	Literature reviews and commentaries
Articles written in English	Articles not written in English
Study participants were HIV-infected children (18 years of age and under)	Study participants were HIV-infected adults (>18 years of age)

### Information sources and search

A comprehensive search strategy was designed in collaboration with a librarian from Stellenbosch University Library (Cape Town, South Africa). The databases searched included EBSCOhost research, Pubmed, Web of Science and Scopus. Within the EBSCOhost research database the following databases were accessed: Academic Search Premier, Africa Wide Information, CINAHL, Health Source: Nursing/Academic edition & MEDLINE.

These databases were searched using a combination of keywords including HIV, auditory processing, hearing and child. The keywords or MeSH (Medical Subject Headings) terms were adapted according to the indexing of the database. While HIV is often associated with

AIDS in the literature, preliminary testing of the search strategy identified that the inclusion in the search of the term 'AIDS' identified many irrelevant articles (e.g. where aids referred to assistive devices). This term was then removed from the search on the understanding that its absence in connection with HIV would not diminish the search parameters.

### **Study selection**

Studies identified by the search were first screened for duplicates, then for relevance. A three-step process was followed: the title was first checked for articles that were clearly not relevant for the purposes of the review (e.g. *Management of therapeutic hypothermia for neonatal hypoxic ischaemic encephalopathy in a tertiary centre in South Africa* was excluded, as it was not relevant to the focus of the review). Of the retained articles after this step, the abstracts were then read and further exclusions were made in line with the exclusion criteria (e.g. *Auditory Impairment in HIV-infected individuals in Tanzania* was excluded as it related to the adult population and did not report on a specific auditory processing skill). Articles were then read in full text, and retained if they focused on measurements of auditory processing skills in children who were HIV positive (Fig 1). Reference lists of the retained articles were then searched for additional studies that may not have been identified by the primary search. As a final step, an international expert on auditory processing was consulted on whether the auditory skills identified from each article, were correctly identified.

### **Data collection process**

A data extraction sheet (Table 2) was developed and used to extract data from included articles. The data collection sheet included: author, year, study design, level of evidence, study setting, description of the sample, assessment measures used in each study, auditory processing skill as described by the ASHA [19] and key findings. All stages of the review were conducted by two authors (EO & HE) who worked independently. Findings were then

compared, and any discrepancies were discussed and resolved by EO and HE. A third author (GD), who also collated the results, was consulted when a discrepancy could not be resolved.

### **Hierarchy of evidence**

Study design was classified according to the Joanna Briggs Institute (JBI) levels of evidence [30].

### **Assessment of risk of bias**

Methodological quality of included studies was not evaluated due to the scoping nature of the review [29].

### **Synthesis of results**

Data was summarized for currency, country of origin, method of assessing auditory processing skills and key outcome measures using tables, figures, numerical analysis and narrative synthesis, as recommended by Arksey and O'Malley [26].

### **Additional analyses**

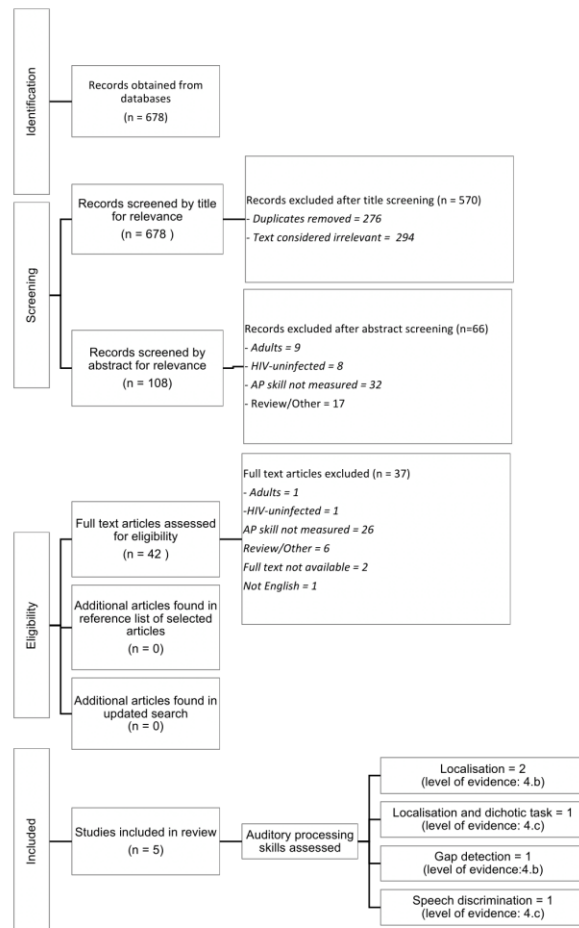
By examining the scope of research described in each article, this enabled the authors to identify gaps in literature and areas for further research.

## **Results**

### **Study Selection**

Fig 1 outlines the study selection process. A total of 678 articles were found in the selected databases. After titles were screened for relevance and duplicates were removed, 108 articles remained. Abstracts of these articles were then screened, according to the inclusion and exclusion criteria (Table 1) and resulted in 42 articles being included for full text review. Following full text review, 37 articles were excluded as they did not meet inclusion and

exclusion criteria (Table 1). The remaining five articles [5,23,24,31,32] were retained for this review. Table 2 summarises key characteristics of each article. No additional articles were found during the search of relevant reference lists.



**Fig 1. Flowchart depicting study selection process**

## **Study characteristics**

The studies were all cross-sectional designs, whose subjects ranged in age from 1 month to 16 years. Although the study sample sizes ranged from 15 to 244 children, auditory processing skills were not measured in all the subjects. Three of the studies included control groups [23,24,32], while two studies reported case series [5,31]. The studies were all conducted in urban settings, in developing countries, with three of the studies based in Brazil (South America) and the other two studies based respectively in Tanzania (Africa) and Mexico (North America). Table 2 provides a summary of the included studies, and Table 3 summarises the reference population and the sample.

**Table 2:** Key characteristics of included articles as these relate to Auditory Processing Skills

Author(s)	Title	Study design (Level of evidence)	Study setting	Participants (Patient)	Assessment measure (Intervention)	Auditory processing skill (ASHA, 2005) (Outcome)	Key findings
Matas, Sansone, Iorio, & Succi (2000)	Audiological evaluation in children born to HIV positive mothers	Cross sectional  Case-control  (Level 4.b)	São Paulo, Brazil (urban)	143 children aged 1 month to 30 months (HIV+ = 18, HEP = 34, HEU = 91)	BOA (size of response, timing of response, attention to sound, lateralization, localization in vertical plane, cochlea-palpebral reflex)	Binaural interaction (lateralization/localization)	Central auditory impairment observed more often in HIV+ group than in two control groups. In HIV+ group, findings suggestive of central auditory disorder observed more frequently than findings indicating middle ear involvement.
Matas, Iori, Succi & Cecília (2008)	Auditory disorders and acquisition of the ability to localize sound in children born to HIV-positive mothers	Cross sectional  Case-control  (Level 4.b)	São Paulo, Brazil (urban)	143 children aged 1 month to 30 months (HIV+ = 18, HEP = 34, HEU = 91)	BOA (size of response, timing of response, attention to sound, lateralization, localization in vertical plane, cochlea-palpebral reflex)	Binaural interaction (lateralization/localization)	Significant difference between HIV+ group and two control groups with regards to acquisition of ability to localise sound.
Palacios, Montalvo, Fraire, Leon, Alvarez & Solorzano (2008)	Audiologic and vestibular findings in a sample of Human Immunodeficiency Virus type-1-infected Mexican children under highly active antiretroviral	Cross sectional  Case-series  (Level 4.c)	Mexico City, Mexico (urban)	23* HIV+ children aged 5 months to 16 years  No control group	Speech discrimination (9 participants)	Auditory discrimination	Abnormalities in speech discrimination observed in 4 children: 2 suggesting conductive involvement, 1 cochlear involvement and 1 central involvement observed in 1 child

	therapy						
Maro et al. (2016)	Auditory impairments in HIV-infected children	Cross sectional  Case-control  (Level 4.b)	Dar es Salaam, Tanzania (urban)	244* children aged younger than 18 years (HIV+ = 131, HIV- = 113)	Gap detection (HIV+ = 48, HIV- = 19) sample size as reflected in Results section and not in Abstract	Auditory temporal processing and patterning	No significant difference in gap detection thresholds and ABR latencies between the HIV infected and control children. ABR latencies for HIV- group reflected in text 0.1msec longer than latency reflected in Results section.
Romero, Alfaya, Gonçalves, Frizzo & Isaac (2017)	Auditory alterations in children infected by Human Immunodeficiency Virus verified through auditory processing test	Cross sectional  Case series  (Level 4.c)	Sao Paula, Brazil (urban)	15 children aged 8 to 9 years  No control group	SSW, SAPT (sound localization in 5 directions, memory for verbal sounds, memory for nonverbal sounds)	Binaural integration (dichotic speech), binaural interaction (localisation)	Auditory changes, related to auditory processing, observed. Difficulties observed related to deficits in attention, memory and auditory figure ground skills. 8-year olds performed poorer than 9-year olds suggesting a maturational effect.

\*Total number of children who underwent audiological assessment, not necessarily auditory processing assessment; HIV+ = children infected with HIV; HIV- = children who are HIV negative; HEU = children who have been exposed to the virus but are uninfected; HEP = children who have been exposed to the virus and are positive but their status has not been confirmed due to their age.

BOA = behavioural observation audiometry, SSW = staggered spondaic words, SAPT = simplified auditory processing

**Table 3:** Reference population and sampling approach

Study	Nationality	Reference population	Source	HIV diagnosis	Age
Palacios et al 2008	Mexico	HIVP children < 17 years	AIDS outpatient clinic	All infected	5mths - 17 years
Matas et al 2000	Brazil	Children born to HIV-infected mothers	Department of Pediatrics	HIV children (I), serum-reverted (SR) and exposed to HIV (I).	1mth-2.5yrs
Romero et al 2017	Brazil	Children with HIV	Not stated	All infected	8 or 9 years
Matas et al 2008	Brazil	Children born to HIV-infected mothers	Department of Pediatrics	HIV children (I), serum-reverted (SR) and exposed to HIV (I).	1mth-2.5yrs
Maro et al 2016	Tanzania	HIVP children < 18 years	Pediatric Program at Infectious Disease Center	HIV+ children and HIVN family members	0.8 yrs-to 18 yrs

## Synthesis of the results

### Sampling issues

The five papers reported on four datasets, with Matas et al (2000, 2008) reporting on different aspects of the same sample. The study samples differed in selection criteria, age and health status. Although four papers reported on the sampling location, information on how children were selected for study participation was notably absent in all studies. Overall, the included papers report on 185 HIVP children (cases), of a total of 425 children. All cases were on ART. Within the 240 non-HIVP (control) children were 78 serum-reverted children and 30 HIV exposed children, who were treated separately in subgroup analysis (Matas et al 2000, 2008). Maro et al (2016) recruited 113 HIVN (control) children who were family members of cases (Maro et al 2016). Whilst four studies excluded children with comorbid medical



conditions, Maro et al (2016) included 31 HIVP and 3 HIVN children with TB histories. The overall sample age ranged from one month to 18 years, however it was not possible from the available information to estimate an average sample age. On the available data, it might be presumed that the majority of children were younger than 10 years. Palacios et al (2008) reported on 23 Mexican cases (average age 4.5 years); Matas et al (2000, 2008) reported on a dataset of 143 children born to HIVP mothers (all children being younger than 2.5 years); Maro et al (2016) reported on 244 children (cases and controls) of average age 10.1 years, and Romero et al (2017) reported on 15 cases aged 8 or 9 years. Sample heterogeneity potentially underpins the lack of consistency in the findings of this review.

### **Auditory processing testing procedures**

The studies described different test procedures, namely Behavioural Observation Audiometry (size of response, timing of response, attention to sound, lateralization, localization in vertical plane, cochlea-palpebral reflex) (Matas et al 2000, 2008); speech discrimination (Palacios et al 2017); gap detection thresholds (Maro et al 2016); and Staggered Spondaic Words, Simplified Auditory Processing Test (sound localization in 5 directions, memory for verbal sounds, memory for nonverbal sounds) (Romero et al 2017).

### **Auditory processing skills**

Moreover, the test procedures described in the studies assessed different auditory processing skills. Four clusters of skills, described below, were identified during data extraction: (1) binaural interaction (Matas et al 2000, 2008, Romero 2017); (2) auditory discrimination (Palacios et al 2017); (3) auditory temporal processing (Maro et al 2016) and (4) binaural integration (Romero et al, 2017).

- **Binaural interaction:** Localisation, as a measure of binaural interaction, was assessed in three studies [24,31,32]. A higher occurrence of abnormal findings in the HIV-infected group, compared to the two uninfected groups, was reported by Matas et al [24,32] while Romero et al [31] reported that localisation difficulties occurred in less than 30% of their participants.
- **Auditory discrimination:** The only study that assessed auditory discrimination skills [5], reported that abnormal findings were observed in four children in a sample of nine. The origin of the deficits was attributed to conductive involvement ( $n = 2$ ), cochlear involvement ( $n = 1$ ) and central involvement ( $n = 1$ ).
- **Auditory temporal processing:** Maro et al [23] reported on gap detection thresholds as the outcome measure for auditory temporal processing. The authors reported that the mean and median gap detection thresholds, between children infected with HIV ( $n = 48$ ) and uninfected children ( $n = 19$ ) were not significantly different.
- **Binaural integration:** One study assessed binaural integration by using the Staggered Spondiac Word Test (SSW) [31]. Although 87% (13 of the 15 participants) of children presented with difficulties, these difficulties were attributed to problems in the areas of attention, memory and auditory figure-ground skills rather than only problems with binaural integration.

## Discussion

This is the first scoping review that we know of, that describes the volume and nature of research relating to auditory processing skills in HIV-infected children. We believe that our scoping review search strategy was sufficiently comprehensive that we identified all available evidence in this area. The strength of the scoping review was enhanced by having two

independent researchers undertake the screening and extraction steps. Moreover, the scoping nature of the review enabled the identification of all available literature in this area without the restraints of seeking specific research designs or methodological quality. It thus provided a comprehensive overview of the literature currently available on the topic.

From the limited available literature, there is consistent evidence of deficits in the auditory processing skills that were assessed in HIV-infected children [5,23,24,31,32]. The review highlights that the published research is limited in numbers of studies (five), study designs (cross-sectional), geographical settings (urban, developing countries).

A possible reason for the limited research on auditory processing in the HIV-infected paediatric population, is the lack of consensus between researchers on definitions and/or descriptions of auditory processing [33]. Various definitions have been postulated with the definition by the American Speech-Language-Hearing Association [19] being the most widely cited. According to this definition, (Central) Auditory Processing is *“the perceptual processing of auditory information in the CNS and the neurobiologic activity that underlies that processing and gives rise to electrophysiologic auditory potentials”*. More recently, the British Society of Audiology [34] has described auditory perception as being *“the awareness of acoustic stimuli, forming the basis for subsequent action”* and *“results from both sensory activation (via the ear) and neural processing that integrates this ‘bottom up’ information with activity in other brain systems (e.g. vision, attention, memory)”*.

The literature identified in this review identified limitations in the scope of assessment measures for auditory processing skills. The use of assessment measures as a reflection of a specific skill, is complex. A gold standard for the assessment of auditory processing disorders does not exist, although various assessment guidelines recommend that a test battery

approach be used and that an auditory processing deficit cannot be diagnosed on the basis of one test, measuring a single auditory processing skill [19,35–38]. The American Speech-Language-Hearing Association [19] lists various categories of central auditory tests that may be considered for the assessment of central auditory processing including: auditory discrimination tests, auditory temporal processing, dichotic speech tests, monaural low-redundancy speech test, binaural interaction tests, electroacoustic measures and electrophysiologic measures. Despite the variety of assessment measures available, four of the five studies included in the review, only reported on measures that were easily quantifiable and not language-dependant, such as auditory discrimination, localization and gap detection thresholds.

Auditory temporal processing do not appear to be affected by HIV [23]. Maro et al. [23] did not report significant differences in gap detection thresholds between HIV-infected and uninfected children. Furthermore, similar performances were reported for HIV-infected children regardless of the type of ART being used or the time delay before initiation of treatment [23]. A possible reason for the lack of statistically significant results was the small sample size [39] as very few children could complete the task due to the complexity of the instructions. Despite similar results being reported for adults when HIV-infected and uninfected individuals were compared [40], within the group of HIV-infected adults, persons using antiretroviral therapy (ART) performed significantly poorer than persons not using medication [40]. Based on the findings of this adult study, a possible explanation for deficits in gap detection is the use of ART, rather than the virus itself. However, the two groups that were compared in the adult study also differed in term of mean age and history of tuberculosis [40] and both these factors have been associated with auditory dysfunction [41,42].

Research suggests that HIV may affect auditory discrimination. The only study that used this skill as an outcome measure, reported that 44% of the sample presented with deficits [5]. However, this study was a case series with a small sample size (nine participants). Although the authors differentiated between conductive, cochlear and central impairment; the inclusion of children with hearing loss may have increased the prevalence of abnormal findings as hearing loss has been associated with impaired speech perception abilities [43].

Binaural interaction skills appear to be impaired in HIV-infected children. This can be seen in deficits in localizing abilities [24,31,32]. However, the extent to which these abilities are affected is not known as one of the studies was a case series [31] which provides limited information about causality and the pattern of the auditory processing deficits [39]. The other studies were case-control studies [24,32] that did not report on the statistical significance of the observed differences. A factor that may have contributed to the prevalence of impaired localizing skills is age, as two of the studies [24,32] assessed babies and infants (interrogating the same sample of children born to HIVP mothers). Muir et al. [44] reported that the development of localizing skills followed a u-shaped trajectory. According to this trajectory, a neonate's response to sound decreases between the ages of one and three months with a greater, more accurate response being seen from four to five months of age [44].

Binaural integration is reported to be abnormal in HIV-infected children. The findings reported by the one study that assessed performance on a dichotic speech test [31] are consistent with the findings reported for a study conducted in HIV-infected adults [45]. However, when considering the well-documented neurocognitive effects of HIV [46,47], it is difficult to comment on whether it is a pure binaural integration deficit as this skill is so intimately entwined with executive functions, in particular attention and memory [48].

The biologic sequelae of HIV have been well-documented in children, and the studies included in this review provide insights into a few auditory processing skills that are affected in HIV-infected children. These studies use methodologies that answer questions related to the organic nature of HIV and provide information on the deficits that may be associated with HIV. However, when one considers the chronic nature of the virus, these methodologies may need to be supplemented with measures to answer questions related to functional outcomes of HIV. In order to provide appropriate educational services, identifying deficits that may affect learning is not enough, as understanding how these deficits affect the way the individual functions in their learning environment, is also needed.

### **Limitations**

The review findings highlight the scarcity of research in this area. We were concerned that the inclusion of only English language studies may have introduced bias toward countries from Europe and North America, however, all the articles were from countries whose official languages were not English. The exclusion of conference abstracts and other grey literature may have also introduced publication bias; however, this literature may not have provided the detail that we required in order to describe research in the area.

### **Conclusion**

This systematic scoping review identified only five studies on auditory processing skills in HIV-infected children and highlights the paucity of research in the area. This evidence-base is inconclusive regarding the association between HIV and auditory processing difficulties as the studies did not necessarily assess the same auditory processing skill and findings were, therefore not comparable. In order to better understand the impact of the virus on learning and to justify the inclusion of auditory processing assessments in the basic health and

educational services offered to children infected with HIV, further research of all auditory processing skills is needed. Carefully designed case control studies looking at the time-sequence and relationship between HIV, auditory processing and learning in children should be considered. As the organic consequences of HIV have frequently been demonstrated, it is imperative that future studies include functional outcomes so as to develop a more comprehensive picture of the auditory abilities of this population. Furthermore, research needs to address issues of sampling, sample size calculation and heterogeneity of the population, as well as exerting better controls for maturational aspects of auditory processing, by carefully considering the age of both participants and controls.

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## Reflections on Findings

This systematic scoping review highlights the paucity of research into auditory processing capacities in CLHIV. The evidence-base is inconclusive regarding the association between HIV and auditory processing difficulties because the studies did not necessarily assess the same auditory processing capacity or use similar assessment measures. The findings of the various studies were, therefore, not comparable.

The assessment of auditory processing capacities is a perplexing area with a range of available position statements, guidelines, and reports recommended for assessment and management of this disorder. Despite these clinical documents, there is still no universally-accepted test battery that is considered to be the gold standard for diagnosing auditory processing disorders (British Society of Audiology, 2018).

The reviewed studies aimed to describe specific auditory processes in CLHIV and not diagnose an auditory processing disorder. A holistic picture of auditory processing in CLHIV could not be gained as the studies assessed a limited number of auditory processing capacities. The studies varied on how these capacities were measured and included: behavioural observation audiometry (BOA), speech discrimination test, gap detection test, sound localization test, and staggered spondee words.

Although BOA is widely used to assess infants, results obtained by this method may not be accurate (Jerger & Hayes, 1976). Young children may fail to respond or may not respond consistently despite normal hearing (Jerger & Hayes, 1976). In addition, responses may be difficult to observe, and observer bias may affect interpretation of the results (Gans, 1987).

The included studies reported on children as young as one month. However, auditory processing capacities are age dependent as these capacities develop over time (Moore,

Cowan, Riley, et al., 2011). Various position statements and guideline have indicated that behavioural tests of auditory processing capacities may not be valid or reliable for children younger than 7 years (American Academy of Audiology, 2010; British Society of Audiology, 2018; Canadian Interorganizational Steering Group for Speech-Language Pathology and Audiology, 2012). Administering these tests to young children is, therefore, not recommended, as poor performance may be an indication of typical neurodevelopment, rather than the effect of HIV.

Further research of a range of auditory processing capacities is needed to understand the impact of the virus on learning, and to justify the inclusion of auditory processing assessments in the basic health and educational services offered to CLHIV. Carefully designed case-control studies investigating the time-sequence and relationship between HIV, auditory processing, and learning in children, should be considered. As the organic consequences of HIV have frequently been demonstrated, future studies must include functional outcomes to develop a more comprehensive picture of the auditory processing capacities of this population.

Furthermore, research needs to address issues of sampling, sample size calculation, and heterogeneity of the population, as well as exert better controls for maturational aspects of auditory processing, by carefully considering the age of participants.

## Chapter 5

### Methods

This chapter presents the aim and objectives of the study. Furthermore, it outlines the research design, participant selection procedures, ethical considerations, data collection procedures, and data analysis methods used to collect primary data to address the research aim and objectives.

#### Study Aim

The research aim of this study was to analyse auditory functioning (hearing and auditory processing capacities) and learning capacities (namely NVIQ, STM and WM) of pre-teen CLHIV and to compare these to CNLHIV of a similar age and social circumstances.

#### Study Objectives

The study objectives were to:

1. Describe a profile of hearing in CLHIV and CNLHIV;
2. Describe a profile of auditory processing in CLHIV and CNLHIV;
3. Investigate the predictor variables associated with hearing loss in CLHIV;
4. Test the association between auditory functioning (hearing and auditory processing capacities) and learning capacities (NVIQ, STM, WM) in CLHIV and CNLHIV.

#### Study Design

A descriptive cross-sectional research design was utilized for the primary research reported in this dissertation. Descriptive research entails gathering data to obtain a detailed representation of the person, situation, or social setting under investigation (Neuman, 2000). This study is situated within descriptive research, as it aims to describe hearing loss and auditory processing and its relationship to NVIQ, STM, and WM in CLHIV and CNLHIV.

Cross-sectional research was appropriate for this enquiry, which aimed to investigate differences between groups of children at a point in time (de Vos, Strydom, Fouche, & Delport, 2011; Neuman, 2000). In this case, the key focus was to describe overall auditory functioning (hearing and auditory processing) and learning capacities in CLHIV compared to CNLHIV. The advantage of using this design was that data could be collected over a short time while still supporting the analysis of different combinations of Exposures and Outcomes (Neuman, 2000).

## **Participant Selection**

### **Setting**

One large tertiary metropolitan hospital in Cape Town provided access to CLHIV attending its Infectious Diseases Clinic (IDC). This hospital provided services for over 3.4 million people in surrounding socioeconomically disadvantaged suburbs, most of whom relied on public health care. In South Africa, only 17% of citizens are estimated to have medical insurance, resulting in the majority attending public health facilities (Statistics South Africa, 2018a). Although a tertiary hospital is a public hospital to which more complicated cases are referred, in this instance, the participating hospital also provided an ART clinic (Infectious Diseases Clinic) to patients who were unwilling to be transferred to the local community-level health facilities.

### **Sample and Sampling Method**

**Sample.** This study investigated school learners aged 9-12 years who had confirmed HIV-positive status (CLHIV) or had documented evidence of HIV-negative status (CNLHIV). The sample was not age- or gender-matched because of recruitment issues.

**Sampling:** A nonprobability, purposive sampling approach was used to select the places from which CLHIV (tertiary hospital IDC) and CNLHIV (full-service school where



children's HIV status was known) were recruited. Purposive sampling of places of recruitment was the most suitable sampling procedure for this study in this sociodemographic area as it allowed the primary researcher to efficiently identify the subjects required to address the aims and objectives of the study (Daniels, 2012). Comprehensive sampling was then undertaken at each site, by inviting all eligible CLHIV attending the hospital IDC, and all eligible CNLHIV attending the primary school, to enter the study. This sampling procedure enabled the researcher to ensure that all potentially relevant participants were offered the opportunity to join the study (Table 1).

*Inclusion and Exclusion Criteria.* Table 1 describes the eligibility criteria used for the selection of participants and the rationale for each criterion.

**Table 1:** *Eligibility Criteria for Participants*

<b>Selection Criteria</b>	<b>Requirement</b>	<b>Rationale</b>
Age	Aged 9-12 years	This age group was selected to ensure that the participants were not too young to complete the auditory processing test battery. Literature indicates that auditory processing test batteries may not be appropriate for younger children, as auditory processing skills are acquired developmentally (Moore, Cowan, Riley, et al., 2011; Moore, Ferguson, Edmondson-Jones et al., 2010). The maximum age of 12 years was selected as this age corresponds to the widely accepted definition of a school-aged child (i.e. 5-12 years) (Erikson, 1959 cited in McLeod, 2008). The inclusion of participants in this relatively small age range limited the effect of maturation on the performance of the children.
Population group	Participants from any population group	No limitations were prescribed for this criterion in order to obtain a representative sample.
Gender	Male and female	No limitations were prescribed for this criterion in order to obtain a representative sample.
Language proficiency	Proficient in Afrikaans, English, or isiXhosa.	The inclusion of these three official provincial languages (Western Cape Government: Department of Cultural Affairs and Sport, 2019) allowed for a more representative sample and reduced the risk of discriminating based on language.
HIV status	CLHIV were included if they had been diagnosed as HIV positive. CNLHIV were included based on reported negative status.	The aim of the study was comparisons of CLHIV and CNLHIV
Schooling	Participants were required to be enrolled in primary school, at least in Grade 3, at the commencement of the study.	The study aims to investigate “learning”. Primary school children typically have one educator who is responsible for teaching the bulk of the curriculum. As one of the data collection procedures involves the completion of a questionnaire by the educator, this measure was included to facilitate the data collection procedure as only this one educator would be included in the study.
Comorbidity	Participants who presented with diagnosed comorbid medical conditions affecting cognitive abilities were excluded.	The study aimed to investigate the capacity for learning, as observed by NVIQ, STM, and WM. The exclusion of these conditions facilitated interpretation of the findings, as comorbid cognitive deficits were eliminated as confounders.

Males and females were included if they had: (1) documented HIV-positive status or reported HIV-negative status; (2) were aged between 9 – 12 years; (3) had verbal proficiency in at least one of English, Afrikaans or isiXhosa (African) language; (4) were enrolled in at least Grade 3 in a mainstream primary school and (5) could understand and complete an assent form. Exclusion criteria were: (1) HIV status not documented/reported; (2) comorbid conditions causing cognitive impairment (e.g., neurological conditions) that could affect the understanding of, and performance in, the assessment batteries; (3) cognitive impairment (e.g. intellectual disability) that could affect understanding of and performance on the assessment test batteries; or (4) on a waiting list for, or enrolled in, a school for learners with special education needs.

**Recruiting CLHIV.** The IDC at the participating tertiary hospital had records of 836 patients on ART at the end of February 2017. This included 412 children (aged 0 to 18 years), of which 110 fitted the age criteria for the study. Attempts were made to recruit all 110 children on the register attending the IDC for their medical follow-up appointments, between June 2017 and November 2018. The recruitment process involved the primary investigator regularly attending the IDC and physically identifying and recruiting age-eligible children on each clinic day. The IDC operated from Monday to Wednesday (8h00–13h00), with the majority of paediatric appointments available on Tuesdays. Each morning, the medical records (folders) of all children with appointments for the day were accessed by the primary investigator at the IDC, and she identified all potential candidates based on their date of birth. Caregivers accompanying children to their appointments were approached and informed of the study. Caregivers who were interested in the study, were asked questions related to the eligibility criteria (e.g. *Which school does your child attend?*) (Table 1). If all the inclusion criteria were met and the attending caregiver consented, the child was enrolled

in the study. A small reimbursement for travelling costs was offered to each family to assist them to return for the study appointment.

**Recruiting CNLHIV.** Participants were recruited from one local primary school in the same area as the participating hospital. Information pamphlets (addressed to the caregivers) were distributed to 162 children aged 9-12 years in the school, together with informed consent forms and the primary investigator's contact telephone number. The school was classified as a Full-service school, which is defined in the *Education White Paper 6* as "schools and colleges that will be equipped and supported to provide the full range of learning needs among all learners" (Department of Education: ELSEN Directorate, 2001, p. 22). The children's HIV status was thus known to school management. The school principal assisted the primary investigator in distributing research information only to children who were known not to be HIV positive.

**Sample Size Calculation.** Sample size calculation was undertaken using EpiInfo Version 7.2.2.6 (Dean et al., 2011). Based on an estimated prevalence of hearing loss in CLHIV (33%), estimated prevalence of hearing loss in CNLHIV in low socio-economic conditions (15%), 80% power, and 95% Confidence, 174 children were required in total. The estimated prevalence of hearing loss reflected the prevalence most often reported in the systematic review of 21 studies, which included 11 paediatric studies, conducted by Ensink & Kuper (2017).

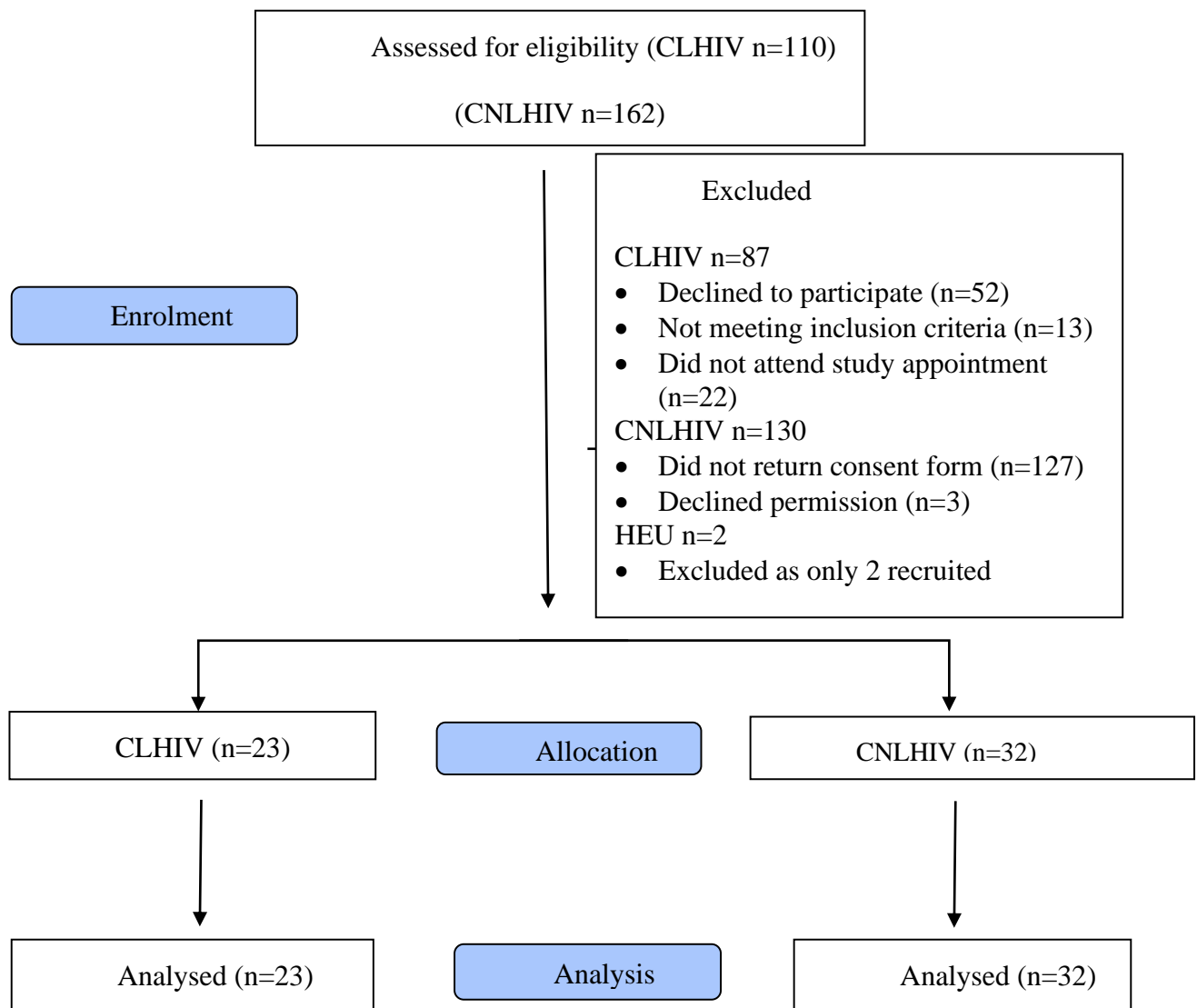
**Sample.** Two hundred and seventy-two children were identified as potential study participants.

**CLHIV.** One hundred and ten potential participants were identified at the IDC. All were individually invited to participate, in person, by the primary investigator, by speaking to the accompanying caregiver. Fifty-two children's caregivers declined the invitation to

participate, 12 children agreed to participate but did not meet the inclusion criteria and 22 children whose caregivers agreed for them to participate, did not attend their study appointment (even after reminders were sent or appointments were rescheduled). This left 23 eligible CLHIV whose caregivers consented for them to participate and who did so.

**CNLHIV.** Thirty-seven consent forms were returned out of the 162 information pamphlets and consent forms distributed at the participating school (to preteen children known to be HIV negative). Out of these, three parents declined their child's participation. On scrutinising the potential participants' information, it also became clear that two CNLHIV had been exposed to HIV, although they were not HIV positive (5.4% of the sample). Their data were excluded from analysis as the numbers were too small for separate subgroup consideration. However, these children were tested to ensure equity in access to health assessments. This left 32 eligible CNLHIV whose caregivers consented to their participation.

Thus, the study dataset consisted of 55 participants (23 CLHIV (42.8%) and 32 CNLHIV (57.2%)). Figure 3 outlines the study inclusion and exclusion flow diagram.



**Figure 3. Flow Diagram Depicting Study Inclusion and Exclusion**

### Demographics

**Age.** The average age of the overall sample was 11.2 years (SD 0.9). The small standard deviation reflected the study inclusion criteria of 9-12-year olds. There was no significant age difference between CLHIV (mean age 11.4 years (SD 0.8)) and CNLHIV (mean age 10.9 (SD 1.2)) (F value <sub>(1)</sub> 3.3  $p > 0.05$ ).

**Gender.** Of the 55 participants, 30 were males (54.5%) and the remaining 25 (45.5%) were female. There were no significant differences in gender proportions in the overall sample, or between CLHIV and CNLHIV ( $p>0.05$ ). Sixteen of the 30 males (53.3%) and 16 of the 25 females (64.0%) were CNLHIV.

**Population group.** Population groups were identified from hospital or school records or by their parents on the case history forms, as Coloured (which predominated (79.8%)), with smaller percentages of children identified as Black (19.1%) or White (1.1%).

**Language.** For this study, participants were described by the languages they spoke at home and school, rather than by population group, which is a contentious issue in South Africa (Khalfani & Zuberi, 2001).

English was the primary home language of 28.9% of participants, while Afrikaans was the primary home language of 46.7% of participants. The remainder (24.4%) spoke an African Indigenous language. The language distribution for the sample followed a similar trend to the provincial language distribution reported for the Western Cape in the South African Census 2011 (Statistics South Africa, 2011), where 20.2% of the provincial population spoke English, 49.7% of the population spoke Afrikaans, and approximately 27.5% of the population spoke an African Indigenous language. By considering the primary language spoken at school, 44.4% spoke English, 46.7% spoke Afrikaans, and 8.9% spoke isiXhosa (an African Indigenous language). Most participants spoke the same language at home and school (87.5%). However, approximately 1 in 6 participants spoke a different language at home and at school. The majority (81.2%) of these spoke an African Indigenous language at home.

English as a primary language was spoken both at home and school by 31.7% of the sample; Afrikaans as a primary language was spoken both at home and school by 31.7%

sample; and IsiXhosa (an African Indigenous language) was spoken as primary language both at home and school by 7.9% of the participants. No English-speaking participants reported a difference between home and school language. Home-school language difference was reported by one of the 21 participants whose home language was Afrikaans (4.8%), and seven of the 11 participants who spoke an African Indigenous language (63.6%).

***Antiretroviral Therapy (ART).*** All CLHIV had been treated with ART at some stage in their lives, although not all had been treated since birth, or since diagnosis (whichever came first). Six participants (28.6%) had a history of defaulting on ART, which potentially reduced their capacity to avoid opportunistic infections. Out of the 22 CLHIV for whom information on ART was available from hospital records, the mean percentage of lifetime exposure to ART was 78.5% (SD 20.7%) (range 23-6% - 100%), with N=10 (43.5%) participants having a lifetime exposure of less than 75%. All participants were on HAART which meant that they were using a combination of ARVs. Twenty-two of the participants (95.6%) were taking Lamivudine (3TC); 21 (91.3%) were taking Abacavir (ABC); 16 were taking Aluvia (69.5%); 7 (30.4%) were taking Efavirenz (EFV); and one each were taking Tenofovir Disoproxil Fumarate (TDF) and Zidovudine (AZT).

## **Ethical Considerations**

Ethical approval (S15/10/220) was obtained from the Health Research Ethics Committee, Stellenbosch University (Appendix E).

Permission was also obtained from:

- Western Cape Department of Health (WC\_2016RP50\_968) (Appendix F)
- Western Cape Department of Education (Appendix G)
- Relevant tertiary hospital (Appendix H)
- The relevant school (verbal permission received from the principal)



The study followed the research ethics guidelines as required by the HREC (Stellenbosch University) and in the document “*Ethics in Health Research: Principles, Processes, and Structures*” (Department of Health, 2015).

*Informed Consent:* Informed consent was obtained before inclusion in the study. For CLHIV, the relevant information was explained to the caregiver of the participant in the language of their choice. As the primary investigator was only proficient in English and Afrikaans, a translator was available for all participants who spoke an African Indigenous language. However, none of the caregivers made use of the translator as they all reported that they were proficient in English. The caregivers were provided with copies of the relevant documentation after the consent form was signed (Appendix I). For CNLHIV, a contact number was provided for the caregivers to contact the primary investigator if they were uncertain about any of the information provided in the information document (Appendix J). This measure was also taken for the teachers. The explanation of the study sent to teachers, excluded the term HIV to prevent unintentional disclosure of the participant’s status. Although the letters to the teachers were sent via caregivers, the caregiver could decide if they were willing to allow teacher participation.

*Assent* was obtained from all participants. The explanation of the study excluded the term HIV to prevent accidental disclosure of the participant’s status.

All participants were provided with the opportunity to ask for clarification if they did not understand the information provided (Appendix K).

*Autonomy:* Participants were informed that participation was voluntary, that they could refuse to participate, and that refusal to participate would not negatively affect them. They were also informed of their right to withdraw from the study at any time without any negative consequences.

*Confidentiality:* Participants were informed that all information obtained during the study would be managed confidentially. Participant numbers were used, thus protecting the identities of the participants. All the information was stored relative to the participant number, and any identifying information was excluded from the dataset. This measure was taken to ensure that the identifying information of the individual participants could not be matched with their HIV status. Although anonymity was strived for by redacting all identifying information of both the participants and research sites, and excluding identifying information in all articles published and during all presentations of the research findings (e.g., scientific conferences), it is acknowledged that the primary investigator was aware of the identity of the participants.

All documentation was stored in a secure place, and all electronic files were password protected. Access to these documents was strictly limited to the primary investigator.

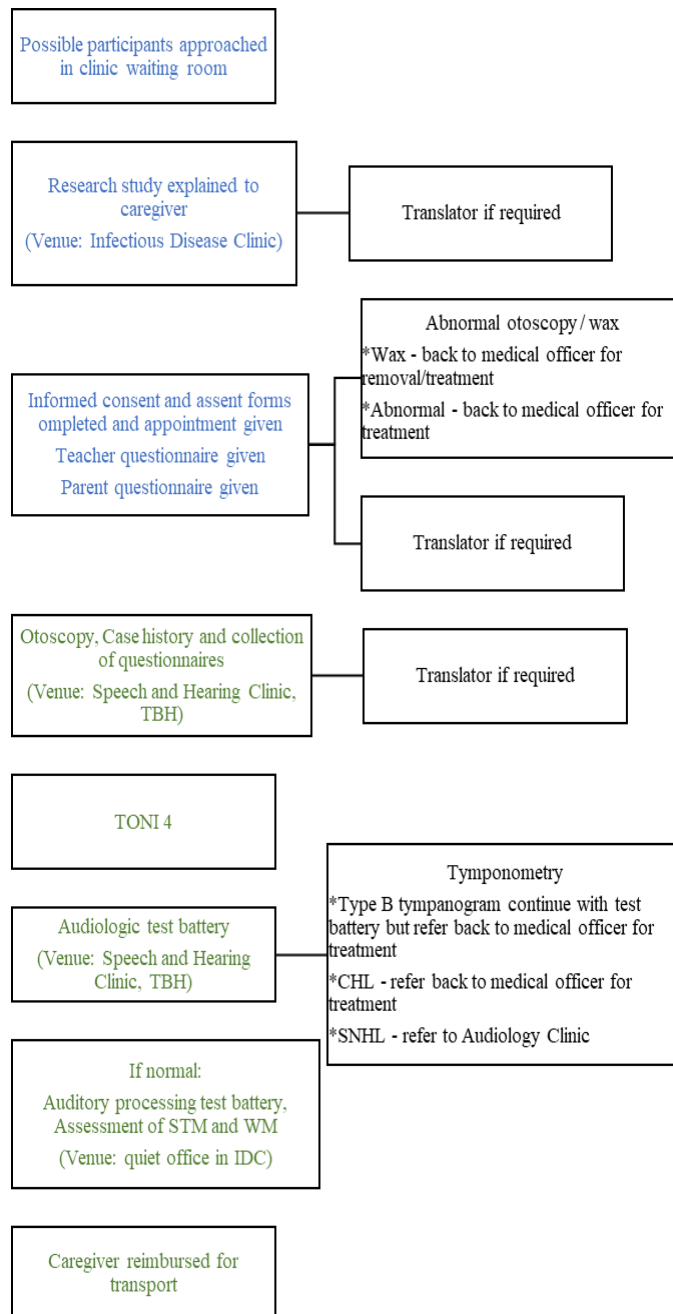
HIV status was not mentioned on information pamphlets and consent forms for teachers, as well as on participant assent forms to prevent unplanned disclosure.

*Distributive justice:* The primary investigator did not foresee any risks of physical harm to any of the participants, or anyone in the research team, and none occurred.

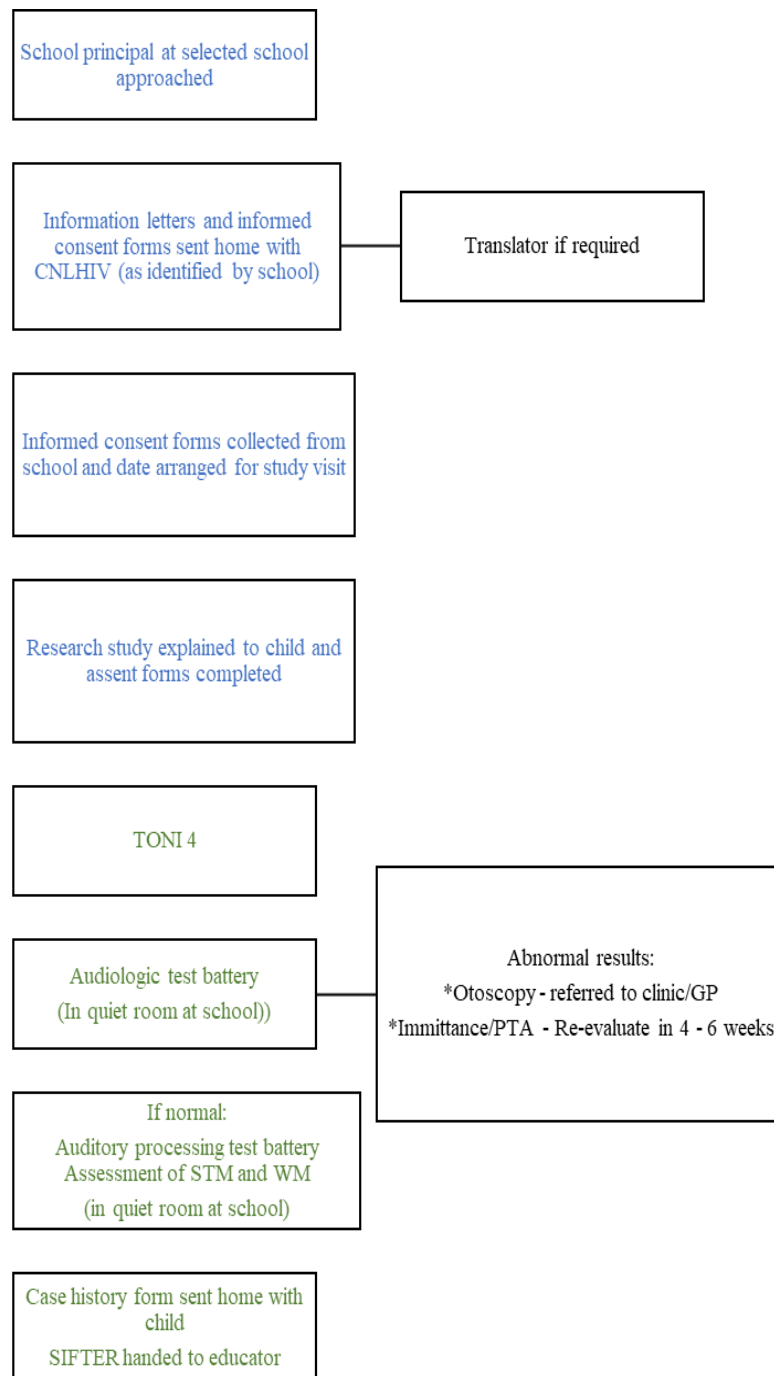
Participants benefitted from participating in the research as all those who were identified as having a hearing disorder were referred for appropriate management (medical or audiological intervention). Although the direct benefit to the individual participant was minimal (knowing their hearing status and being referred for appropriate intervention), the population of CLHIV will benefit from the information generated by this research. This information will be used to provide guidelines for the health and education sectors.

## Procedures

The assessment procedures included assessments of auditory functioning, NVIQ, STM, and WM. The study pathways for the participants are depicted in Figure 4 (CLHIV) and 5 (CNLHIV).



**Figure 4. Study Pathway for CLHIV**



**Figure 5. Study Pathway for CNLHIV**

### *Auditory functioning*

The selection of assessment procedures for auditory functioning was informed by the literature review findings. Auditory functioning was defined as consisting of hearing and auditory processing. Hearing (loss) was primarily assessed by using pure tone audiometry and immittance measures. Auditory processing capacities were assessed using subtests of the SCAN 3C (Keith, 2009a) and the TAPS 3 (Martin & Brownell, 2005). These subtests reflected the discrete auditory processing capacities that are listed in the Technical Report by the American Speech-Language-Hearing Association (2005a).

Three audiologists (GD, HE, EN), who received training in the study procedures before the commencement of the study, conducted all tests.

**Audiologic Test Battery.** The audiologic test battery was conducted on all participants, irrespective of HIV status. All testing was conducted after informed consent from caregivers, and assent from participants had been obtained (Appendices I - K). Audiologic data was collected using a test battery approach. Within the field of Audiology, this approach is considered as standard practice as it allows for the inclusion of various test procedures to gain detailed information regarding an individual's hearing (Cole & Flexer, 2011). Cole and Flexer (2011) further assert that using this approach is advantageous for the following reasons: (1) conclusions about auditory capabilities are not based solely on one test; (2) pathologies can be identified at each of the levels of the auditory system; and, (3) auditory behaviour and functioning can be observed. One of the disadvantages of including many tests within a test battery is that the person being tested may become fatigued during testing, which would affect the reliability and validity of the findings. In order to minimise fatigue, breaks with refreshments were scheduled at regular intervals during the study visit.

The test battery consisted of a case history questionnaire, otoscopy, pure tone audiometry (PTA), and immittance audiometry. Additional tests that were included for CLHIV were: speech audiometry, otoacoustic emissions (OAEs), and auditory brainstem response testing (ABR). These tests were not included for CNLHIV as the equipment was not available at school.

***Case History Interview / Questionnaire.*** The case history is considered to be the initial step in the audiology test battery. Case history for a child typically provides essential information regarding the nature of the auditory complaint, possible contributing factors, developmental progress, communication abilities, and academic achievement (Stach, 2010). The case history interview was conducted within the scope of the study to obtain the relevant health and medical information from the primary caregiver, as well as information on the participant's academic progress and auditory functioning. The information obtained was used to identify potential clinical (such as opportunistic disease) and social risk (such as socio-economic status) factors that would be used during the data analysis phase of the study.

***CLHIV.*** Caregivers were required to complete a written case history questionnaire (Appendix L) while the participants were seen for the basic audiologic test battery. If the caregiver preferred, the complete set of questions was administered verbally in their chosen language (i.e., English, Afrikaans, or isiXhosa). The interview format allowed the primary investigator to probe for answers where necessary, and to clarify any questions that were not understood (Babbie, 2010), although this was only done where the caregiver was non-responsive. The option of verbal administration of the questionnaire ensured that caregivers were not excluded based on literacy levels. The wording of the questions, as it appeared on the questionnaire, was adhered to, to ensure reliability and repeatability. If caregivers

preferred, they could complete the questionnaire at home and return it at the participant's medical follow-up.

*CNLHIV.* The case history questionnaires were sent home with participants as the caregivers were not present during testing. Caregivers were requested to complete the questionnaire and return it to school in a sealed envelope where the primary investigator collected it. Although the primary researcher provided her contact details to the caregivers for any queries or questions, it was assumed that caregivers who were not literate would have access to a literate family member or neighbour.

*Otoscopic Examination.* The otoscopic examination was conducted to investigate the condition of the outer ear and tympanic membrane (Stach, 2010). This part of the assessment was included in the test battery as abnormalities of the outer ear, and the tympanic membrane have been reported in CLHIV (Hrapcak et al., 2016; Ianacone et al., 2017; Smith et al., 2017).

After the procedure was explained to the participant, one of the three audiologists (GD, HE, and EN) who were available at the time, performed the otoscopic examination. A form (Appendix M) was used as a reference to ensure consistency. All relevant structures were examined using a Welch Allyn pocket otoscope. Any abnormalities such as inflammation, growths, foreign objects, excessive wax, or perforations of the tympanic membrane were recorded on the audiogram. If any abnormality was noted, CLHIV were referred to their treating doctor for medical management, while CNLHIV were referred to their closest clinic or private general practitioner via a referral letter.

*Pure Tone Audiometry.* PTA was conducted to determine the behavioural hearing thresholds of each participant as well as the type of hearing loss (Stach, 2010). This

component of the test battery was included as research reports that hearing loss is associated with HIV (Ensink & Kuper, 2017).

*CLHIV:* After the audiologist (HE) explained the procedure, pure tone audiometry was performed in a soundproof audiometric booth, using a GSI 61 audiometer (calibrated as per legislated standards, SANS 10154-2:2012). Circum-aural earphones (TDH-39P) were used, and air conduction thresholds were obtained at 250Hz, 500 Hz, 1000 Hz, 2000Hz, 4000Hz, 8000 Hz as per the Guidelines for Manual Pure Tone Threshold Audiometry (American Speech-Language-Hearing Association, 2005b), for the left and right ears separately. All thresholds were plotted on the participant's audiogram. A participant, who was tested in the audiometric booth, was considered to have a hearing loss if a pure tone average (PTA) of >15dBHL was obtained (Northern & Downs, 2002). Bone conduction threshold testing, using a B71 bone vibrator, was only conducted at frequencies where the air conduction threshold was >10dBHL (Stach, 2010). The bone conduction thresholds were obtained in order to describe the type of hearing loss, i.e. conductive, sensorineural, or mixed hearing loss. The bone vibrator was placed on the mastoid-bone prominence for all participants. The advantages of mastoid placement include slightly improved thresholds, less need for masking and less complicated masking processes (Stach, 2010). Any participant presenting with a sensorineural hearing loss was referred to the Audiology Department at the tertiary hospital for diagnostic testing and further management. Any participant presenting with a conductive or mixed hearing loss was referred to their treating doctor at the IDC, for medical management.

*CNLHIV:* After the audiologist (EN) explained the procedure, pure tone audiometry was performed in a quiet venue, as provided by the school, and testing was completed using an Interacoustics AS608 portable audiometer (calibrated as per legislated standards, SANS



10154-2:2012). Circum-aural earphones (Amplivox Audiocups) were used, and air conduction thresholds were obtained at 250Hz, 500 Hz, 1000 Hz, 2000Hz, 4000Hz, 8000 Hz as per conventional audiometry (Stach, 2010), for the left and right ears separately. All thresholds were plotted on an audiogram. A participant, who was tested in a quiet environment, was considered to have a hearing loss if a pure tone average (PTA) of >25dbHL was obtained (Northern & Downs, 2002). Bone conduction was not conducted.

***Tympanometry.*** Tympanometry was conducted to assess the transmission of sound through the middle ear (Stach, 2010). This component of the test battery was included, as research has reported an increase in abnormal middle ear function in persons with HIV (Ianacone et al., 2017).

After the audiologist explained the procedure, tympanograms were obtained using a GSI Tympstar (CLHIV) (HE) and Interacoustics MT10 (CNLHIV) (EN) with a 226 Hz probe tone. Both machines adhered to legislated calibration standards (SANS 10154-2:2012). The results were recorded on the participant's audiogram, and the following parameters were used to indicate normal middle-ear function: Type A tympanogram with a middle ear pressure of -100 to 100 daPa; acoustic compliance of 0.3 to 1.7 ml; and ear canal volume of 0.4 – 1.5 ml (Stach, 2010). Participants presenting with abnormal tympanograms were referred to the treating doctor (IDC) or their closest clinic for medical management.

***Acoustic Reflex Threshold Testing.*** Acoustic reflex threshold testing was only available for the CLHIV as the equipment was not available at the school. This test was conducted because it provides useful information regarding the possible site of the lesion, i.e., whether the hearing loss is due to a cochlear or retro-cochlear pathology (Northern & Downs, 2002). This component of the test battery was included as ototoxic medication affects the

cochlear (Khoza-Shangase, 2010), and acoustic reflex thresholds are a sensitive indicator of cochlear pathology (Northern & Downs, 2002).

After the audiologist (HE) explained the procedure, the acoustic reflex thresholds were obtained for each ear at 500 Hz, 1000 Hz, and 2000 Hz and recorded on the audiogram, using the GSI Tymptstar (calibrated as per legislated standard, SANS 10154-2:2012). For this study, 4000Hz was not included as responses at this frequency are often absent in normal-hearing persons, and the absence of a response is thus not informative (Northern & Downs, 2002).

***Otoacoustic Emission measurements (OAE).*** Distortion Product Otoacoustic Emission (DPOAE) screening measures were only obtained for *CLHIV* as the equipment was not available at the school. DPOAE provides information regarding the functioning of the cochlear, specifically the outer hair cells (Stach, 2010). This component of the test battery was included as OAEs are considered useful in ototoxicity monitoring (Khoza-Shangase, 2010). After the audiologist (HE) explained the procedure to the participant, the DPOAE measurements were obtained in both ears (at 2000Hz, 3000Hz, and 4000Hz) using the GSI 70 (calibrated as per legislated standard, SANS 10154-2:2012). The measurements were automated, using the GSI default 4 protocol (Grason-Stadler, 2009). Test results were scored as “PASS”, “REFER” or “NOISE” (Appendix N). The results were recorded on the audiogram. Participants presenting with abnormal findings were referred to the Audiology Department for diagnostic testing and further management.

***Speech Recognition Thresholds (SRT).*** SRTs were included to assess the reliability of the pure tone thresholds (Stach, 2010). The speech recognition threshold (SRT) was determined for *CLHIV* only, as their testing set-up allowed for Speech Audiometry to be conducted. After the audiologist (HE) explained the procedure, the SRT was determined

using live voice on the GSI 61 audiometer (calibrated as per legislated standards, SANS 10154-2:2012) and recorded on the audiogram. SRT testing required that bisyllabic words were presented to the participants. The SRT is thus the lowest intensity level, at which 50% of these words are identified (Stach, 2010). For this study, paired digits (e.g. one-ten) were used instead of bisyllabic words when the participants were not familiar with the vocabulary on the South African Spondee word list (Hanekom, Soer & Pottas, 2015). The digits were presented to the participants speaking an African Indigenous language, in English, as they were familiar with numbers spoken in English. The SRT and PTA had to be within 10dB of each other for the pure tone thresholds to be considered reliable.

***Auditory brainstem response testing (ABR).*** Auditory brainstem responses are considered to reflect neural activity from cranial nerve VIII to the midbrain. ABR testing was only available for *CLHIV*, as the equipment was not available at the school. This test was included in the test battery as the evidence suggests that hearing loss associated with HIV may be neural in origin (Matas et al., 2000). After the audiologist (HE) explained the procedure to the participant, the ABR testing commenced. ABR data were obtained bilaterally using the GSI Audera. The participant was instructed to remain quiet and still. Surface electrodes were placed on both earlobes, and at high (vertex) and middle (ground) forehead positions. A click stimulus was presented at a rate of 11.1/sec at 75dBnHL, and both rarefaction and condensation tracings were recorded. Peak latencies for Wave I, III, and V were identified and compared to the clinical norms for the Audera system (Appendix O) (G. Kerr, personal communication, 29 April 2020).

The results were recorded on the audiogram. Any participant that presented with abnormal results was referred to the Audiology Department for diagnostic testing and further management.

**Auditory Processing Test Battery.** In clinical practice, auditory processing test batteries are individualized for the client; thus, all categories of tests may not be included for each client (American Speech-Language-Hearing Association, 2005a). However, as the objective of the study was to describe the auditory processing capacities of CLHIV, rather than to make a diagnosis of auditory processing disorder, the investigative team endeavoured to include tests measuring each auditory processing capacity as listed by the American Speech-Language-Hearing Association (2005a).

During 2016, a review of clinically relevant documents was undertaken to collate recommendations regarding the assessment of auditory processing disorders. These recommendations were used to inform the assessment measures used in the study.

A data extraction sheet (Table 2) was developed to extract information in a standard manner from the included documents. The following data were recorded: (1) organisation, (2) auditory processing area to be assessed, and (3) additional assessment measures. The content of each document was analysed concerning assessment of auditory processing, and relevant information was recorded on the data extraction sheet. Although this review did not follow the methodology of a scoping review, the data was collated and summarized systematically using tables, figures, numerical analysis, and narrative synthesis, as recommended by (Arksey & O'Malley, 2005) for systematic literature scoping reviews.

At the time of the review, Heine and O' Halloran (2015) had recently evaluated clinical practice guidelines. It was, therefore, decided to review the documents included in their evaluation individually. The database search, which is typically one of the initial steps in a review (Arksey & O'Malley, 2005; Levac et al., 2010), was therefore not undertaken as these authors had already completed a comprehensive search of the literature. Thus, the following position statements or clinical guidelines were included for this review:

- ASHA Technical Report: (Central) Auditory Processing Disorders (American Speech-Language-Hearing Association, 2005a),
- American Academy of Audiology Clinical Practice Guidelines: Diagnosis, Treatment, and Management of Children and Adults with Central Auditory Processing Disorder (American Academy of Audiology, 2010),
- Practice Guidance: An overview of current management of auditory processing disorder (APD) (British Society of Audiology, 2011b) and
- Canadian guidelines on auditory processing disorder in children and adults: Assessment and intervention (Canadian Interorganizational Steering Group for Speech-Language Pathology and Audiology, 2012).

Although Heine and O'Halloran (2015) evaluated six documents, it was decided not to include:

- Position Statement: Auditory processing disorder (British Society of Audiology, 2011a) as it did not describe the specific areas to assess; and
- Colorado Department of Education Auditory Processing Disorders: A team approach to screening, assessment & intervention practices (Colorado Department of Education, 2008) as it is based on the ASHA Technical Report (2005) that is included in this review.

The five documents consisted of one technical report, three practice guidelines, and one position statement. These documents were from three countries, namely the United States of America, Britain, and Canada. As can be seen in Table 2, all the documents listed similar auditory processing areas for assessment. The British Society of Audiology (2011b) referred to the assessment areas as listed by the American Speech-Language-Hearing Association (2005a) and included electroacoustic measures (e.g., otoacoustic emissions). The Canadian

Interorganizational Steering Group for Speech-Language Pathology and Audiology (2012) also listed memory as an area to be included. However, memory is considered as a domain that may or may not affect auditory processing as it is not necessarily an auditory process. All documents also recommended that cognitive skills be considered when deciding on the assessment, and when interpreting the results. The review of the clinical documents revealed similar recommendations and all the documents that were published after 2005, referred to the ASHA Technical Report (2005).

**Table 2:** *Summary of Assessment Areas in Auditory Processing Clinical Guidelines*

<b>Organisation</b>	<b>Auditory discrimination</b>	<b>Auditory temporal processing</b>	<b>Dichotic speech</b>	<b>Low redundancy</b>	<b>Binaural processing</b>	<b>Additional assessment (if needed)</b>
American Speech-Language- Hearing Association (2005a)	X	X	X	X	X	Electroacoustic Electrophysiologic
American Academy of Audiology (2010),	X	X	X	X	X	Electrophysiologic
British Society of Audiology (2011b)	X	X	X	X	X	Electroacoustic Electrophysiologic
The Canadian Interorganizational Steering Group for Speech-Language Pathology and Audiology (2012)	X (as part of standard audiometric assessment)	X	X	X	X	Memory Electrophysiologic

The clinical practice guidelines typically listed similar areas of assessment, namely auditory discrimination, auditory temporal processing, dichotic speech, low redundancy speech, binaural processing, and electrophysiology assessment when required. For this study, it was thus decided to include tests that assessed all the areas mentioned in the clinical documents. As South African tests were not available, the following subtests from commercially available tests were included in the auditory processing test battery:

- **Auditory discrimination:** Word Discrimination (WD) subtest from TAPS 3 (Martin and Brownell, 2005);
- **Auditory temporal processing:** Gap detection subtest (GP) from SCAN 3C (Keith, 2009a);
- **Dichotic speech:** Competing words-free recall (CWFR) from SCAN 3C (Keith, 2009a);
- **Low redundancy speech/understand speech in background noise:** Auditory Figure-Ground (+8 dB signal to noise ratio) (AFG) from SCAN 3C (Keith, 2009a);
- **Binaural processing:** Laterality (binaural interaction) as measured by correct identification of ear that the stimulus was presented to during the AFG subtest from SCAN-3C (Keith, 2009a)

Although cognisance was taken of the impact of language on test performance, the purpose of the study was not to diagnose an auditory processing disorder, but rather to compare CLHIV to CNLHIV, with similar language exposure. It was assumed that due to similar language exposure, participants would perform similarly on the tests.



**Document Review and Survey.** When this study was conceptualised, it was planned that additional information on the child's academic performance would be provided through a review of academic documents (Academic report), and the use of a teacher questionnaire (The Screening Instrument for Targeting Educational Risk (SIFTER) (Anderson, 1989)). This could have been used to obtain information regarding five important areas for successful learning within an educational environment (academics, attention, communication, classroom participation, and school behaviour). The advantage of using the SIFTER would have been that the participants would be rated by a teacher who was familiar with both the curriculum and child, relative to the performance of their class peers, rather than norms. However, teachers were reluctant to engage with this study for a variety of reasons (for instance, lack of interest, lack of time, difficulty in actually providing information on the child because of classroom workload), and thus collating this information for cases or controls was not possible. Furthermore, some parents were reluctant to give the questionnaire to the teacher for fear of inadvertently disclosing their child's HIV status.

***Retrospective Medical File Review.*** The retrospective medical file review was undertaken to gather further medical information on documented clinical risk factors, including WHO status, CD4 count, ART medication being used, TB history, opportunistic disease, other medication administered and history of middle ear pathologies. Patient records were available for review on medical appointment dates. The primary researcher perused the records and recorded all relevant available information on the data capturing form (Appendix P). Where the physical record was not available, the electronic patient record was accessed via the electronic patient management system of the hospital.

Categorical data were summarised by using graphs, cross-tabulations, frequency counts, and percentages. Continuous and ordinal data were summarised as means (using the

five-number summary), standard deviations, or 95% Confidence Intervals (CI) (Rumsey, 2010).

Data were reported descriptively using means (Standard Deviations) or percentages, as dictated by the form of the measurement. Odds ratios (95%CI) were applied to binary forms of continuous/ integer variables, and relevant categories of the categorical variables to consider associations. Significant associations were identified as those whose 95%CI did not encompass the value 1.

### **Reliability and Validity**

Reliability reflects whether a measuring instrument or technique yields the same result each time it is applied (Babbie, 2010). The following section describes the measures taken to ensure that data collection was reliable.

The audiologists on the research team were trained on the study protocol and procedures before the study commenced to ensure that the data were collected consistently and reliably. The audiologist who completed the assessment recorded a diagnosis on the audiogram, and the primary researcher cross-checked the diagnosis before entering the data into the database. Furthermore, the medical record review was undertaken by the primary researcher to ensure that the data were collected and recorded consistently. The data were entered into a spreadsheet created in Microsoft Excel (Version 16.20.0), with data validation rules set for the cells. This reduced the likelihood of entering incorrect data. The primary researcher (GD) manually checked the accuracy of data entry into the spreadsheet as per the source document.

All audiological equipment used was calibrated per legislated standards (SANS 10154-2:2012) and a biologic check was done before testing commenced to ensure that the equipment was functioning optimally.

A standard set of questions was used for all the participants to ensure reliability during the case history interview. However, some caregivers preferred to complete the case history questionnaire at home, which limited the opportunity to ask for clarity.

Validity refers to the extent to which a measurement measures what it is intended to measure (Babbie, 2010). In this study, experimenter bias was minimised by having a standard set of questions for the case history and using a test battery approach for assessment of auditory functioning. The study testing procedures were routine clinically accepted procedures and followed the ASHA guidelines (2005b). Although the assessments for auditory processing capacities included subtests of validated assessment instruments, these tests were not validated on the South African population. However, there are currently no validated South African tests that target these processes. The aim of the study was to compare two groups of children from similar socio-economic backgrounds to each other, not to the norms. Thus, it was decided to include the test despite the lack of South African normative data. The inclusion of the NMF and NMR rather than the memory for word subtests eliminated the effect of language on memory. Triangulation of measures was intended as multiple data sources and data collection methods were incorporated into the study. However, the planned triangulation was not possible due to reduced return rates for questionnaires. Using more than one test allowed the investigator to compare the results to see whether they correlated with each other.

## **Data Analysis**

### ***Overview***

The data was described by CLHIV and CNLHIV for demographic variables and outcome measures, using appropriate statistics for continuous, integer, or categorical variables.

## ***Data Management***

**Objective 1.** Describe a profile of hearing in CLHIV and CNLHIV

**Objective 3.** Investigate the predictor variables associated with hearing loss

- a. Lifetime exposure to ARVs;
- b. CDC4 count and viral load;
- c. Gestational age
- d. History of repeating school grades, or absence from school;
- e. History of meningitis, TB or malaria; and
- f. Family circumstances (person in a caregiver role, level of caregiver education, family income).

***Data Management.*** HL was determined by a pure tone average (PTA) of >15dBHL for CLHIV and >25dBHL for CNLHIV (Northern and Downs, 2002). The severity of hearing loss was assessed using the degree of loss (0=none, 1=mild, 2=moderate, 3=unspecified), and calculated as an integer score for both ears.

The relevant continuous predictor variables were divided into binary form for entry into logistic regression models (the value 1 indicating hypothesised high risk).

- Lifetime exposure to ARVs was calculated as the percentage of total years lived on ARV (calculated as the difference between age and age at which ARV commenced, divided by age, and expressed as a percentage). It was hypothesized that >50% lifetime exposure to ARVs was protective of HL because it reduced opportunistic infections;
- CD4 counts less than the median were considered to be high risk for HL;
- Children who were older than usual for their grades were identified as old-for-grade (grade 3 older than ten years, grade 4 older than 11 years, grade 5 older than 12 years,

and grade 6 older than 13 years). Children older than expected in their grade were likely to have repeated a grade at school, usually because of regular absence for illness, living with an HIV-positive adult, or being orphaned (Bandason et al., 2013; Pufall, Nyamukapa, Eaton, et al., 2014);

- Family income lower than R26 256 for a family of four based on the value of the food poverty level of R547 per person per month (Statistics South Africa, 2018b).

Categorical predictor variables were categorized as:

- Viral load (not controlled, versus low or undetectable levels);
- History of defaulting on ARV medications;
- WHO HIV staging (stages 3 or 4 (progressed disease) versus stages 1 or 2);
- History of repeating school grades (Yes/ No), or regular absence from school (Yes/ No);
- History of meningitis, TB or malaria (Yes for any);
- A person in caregiver role (parent, other blood relatives, non-blood relative);
- Level of caregiver education (less than year 9; year 9-10; year 11-12; tertiary).

**Objective 1.** Describe a profile of hearing in CLHIV and CNLHIV

**Objective 4.** Test the association between hearing and NVIQ, STM and WM in the CLHIV and CNLHIV.

- a. HIV status and HL;
- b. HIV status and learning capacities; and
- c. HL and learning capacities.

**Data Management.** The hearing loss was considered as none (0) or as three different types (conductive hearing loss (CHL), sensorineural hearing loss (SNHL), or unspecified) (all coded as 1) in the left or right ear. “Unspecified” referred to hearing loss where the type of hearing loss could not be determined as bone conduction thresholds were not available.

The degree of hearing loss in each ear was recorded as mild (PTA = 25 to 40dBHL), moderate (PTA = 41 to 55dBHL) or severe (PTA = 71 to 90dBHL) (Clark, 1981 in Welling & Ukstins, 2015). The category “unspecified” was used when the hearing testing had not been conducted in a soundproof booth.

A cumulative integer score was determined for hearing loss as the per-child sum of severity scores (hearing loss (*yes, no*) in either ear multiplied by the numeric code given to the severity of a loss. Hearing loss was then applied to models as a three-level variable (no hearing loss, hearing loss in only one ear, or hearing loss in both ears). A total severity score was calculated per child and reported as an integer variable for the analysis of variance models. The higher the severity score, the more severe the hearing loss. For logistic regression modelling purposes, the severity score was split into three independent variables (0 for children without hearing loss), and then at the median value of severity for children with hearing loss ( $>0$  to 2 (mild hearing loss),  $>2$  (moderate or severe loss)). In the analysis, the TONI 4 score was expressed as a percent of the possible total score, which was also split at the median value for modelling purposes.

**Data analysis.** Linear regression models were initially constructed to test the association between severity of hearing loss and learning performance scores to gain the most leverage from the sensitivity of the integer variables, using the Pearson  $r^2$  statistic as an estimate of the strength of association (Katz, 2006). The significant predictor variables

identified in initial testing were individually applied to this model with differences in impact being determined as a significant change in the  $r^2$  statistic.

Univariate logistic regression models were constructed to test the association between binary forms of all variables. HIV status was tested with hearing loss (model 1), learning performance (model 2), and hearing loss and learning performance (model 3). Potential confounders were added to these models in a stepwise manner applying the strongest predictor variable first. Predictor variables were retained in the model if they significantly changed the amount of variance, determined from the chi-square value associated with the Likelihood Ratio, assessed against the critical chi-square value for the degree of freedom associated with the model.

(<https://web.ma.utexas.edu/users/davis/375/popecol/tables/chisq.html>).

For regression purposes, changes in  $\chi^2$  values were determined at  $p < 0.05$ . For one degree of freedom, the critical  $\chi^2$  value is 3.8; for two degrees of freedom, it is 5.9, and for three degrees of freedom, it is 7.8.

**Objective 2.** Describe auditory processing capacities in CLHIV and CNLHIV

**Objective 4.** Test the association between auditory processing and NVIQ, STM and WM in CLHIV and CNLHIV.

- a. HIV status and AP,
- b. AP and learning capacities

**Data Management.** Only those children with no hearing deficits were retained for the analysis. The percentage of total scores for the auditory processing capacities and learning capacities (AFG, CWFR, WD, GD, NMF, NMR, TONI 4) were converted into binary form by splitting them at the median value. The primary language spoken at home and school was

recorded for testing purposes as English, Afrikaans or African Indigenous languages (these being combined because of small numbers).

**Data Analysis.** Factor analysis was first applied to the auditory processing measures (AFG, CWFR, WD, GD, laterality) and the learning capacities (TONI 4, NMF, NMR), to identify underlying composite latent variables. These variables were first tested for normality of distribution to ensure that they were appropriate for inclusion in factor analysis models. Spearman (1904) first developed the notion of factor analysis. Its key concept is that a latent (not measured) variable will underpin several observed (potentially correlated) variables because research participants may express similar patterns of responses in the observed variables. In most instances, the latent factor is abstract, and therefore not readily measured. However, the abstract notion underpinning the latent factor may have multiple measurable elements, which, when combined, can provide a single estimate of the new (latent) variable. Thus, the purpose of factor analysis is to analyse these patterns of responses, identify underlying latent factors, and use each latent factor as a single measure, expressing a combination of observed variables. Factor analysis also weights item responses within each latent factor (called factor loadings). These can be combined and then expressed as an individual score for each person, as an estimate of the latent variable. Factor loadings can be interpreted in the same ways as standardized regression coefficients. If an observed variable has a factor loading of about 0.7, then it can be assumed that that observed variable has a correlation of 70% with the latent factor (a strong relationship). Conversely, if the loading is 0.2, the correlation of 20% with the latent factor is considered to be weak. On this assumption, the rules of correlation are applied when considering the factor loadings, as usually only those variables with loadings over 0.3 are considered as vital within a latent variable (Sweet & Grace-Martin, 2011).



Each factor captures an amount of the overall variance in the observed variables, and statistical programmes that calculate factor analysis usually list factors in order of the amount of variation that each factor explains of the overall variance. The eigenvalue is a measure of how much variance in the observed variables is explained by one factor. As a rule of thumb, any factor with an eigenvalue greater than one explains more variance than a single observed variable.

The weighted auditory processing scores were combined into a new latent variable of per-child overall auditory processing performance, and the weighted learning capacities scores were combined into a new latent variable of per-child overall learning capacities. This was calculated as the cumulative sum of the binary value (1,0) for each variable multiplied by the relevant weighing. Given that scores of 1 indicated poor performance, the higher the composite score, the poorer the child performed overall.

**Influence of Predictor Variables.** The influence of potential predictor variables (HIV status, gender, and primary language spoken at home or school) on the new (continuous measure) latent variables of auditory processing performance and learning capacities was assessed using Analysis of Variance models, with significance reported at  $p < 0.05$ . The association between the new latent variables of auditory processing performance and learning capacities was assessed using a univariate linear regression model, with the strength of the association reported as  $r^2$  value (significance  $p < 0.05$ ).

Univariate logistic regression models were also constructed to test the association between binary forms of the new (composite) latent variables of auditory processing and learning capacities (reported as Odds Ratios (OR), 95% Confidence Intervals (95%CI). If a potential predictor variable was found to significantly influence the mean values of the composite auditory processing or learning capacities, its confounding effect was assessed by

adding it to logistic regression models, and testing whether the Likelihood ratio  $\chi^2$  value changed significantly. This was an expression of the amount of variance in the model explained by the component variables. The significance of the change was determined by whether the amount exceeded the critical amount of change in the  $\chi^2$  value for the number of degrees of freedom in the model.

## Chapter 6

### Results

This chapter reports the findings of the study with regards to auditory functioning (hearing and auditory processing capacities), HIV status, and learning capacities (NVIQ, STM, and WM) in South African preteens. The results are presented according to the objectives listed below (also see Chapter 5):

1. Describe a profile of hearing in CLHIV and CNLHIV;
2. Describe a profile of auditory processing in CLHIV and CNLHIV;
3. Investigate the predictor variables associated with hearing loss in CLHIV;
4. Test the association between auditory functioning (hearing and auditory processing capacities) and learning capacities (NVIQ, STM, WM)) in CLHIV and CNLHIV.

The findings have been reported in the following submitted papers:

#### **Appendix A:**

Dawood, G., Klop, D., Pillay, M., & Grimmer, K. (submitted: 17 September 2019). Hearing loss in a group of HAART-treated 9-12-year-old children from Cape Town, South Africa: A cross-sectional study. *Brazilian Journal of Otorhinolaryngology*.

#### **Appendix B:**

Dawood, G., Klop, D., Pillay, M., & Grimmer, K. (submitted: 19 August 2019). HIV, hearing loss, and learning capacity in Cape Metropole pre-teens, South Africa: A cross-sectional study. *BMC Pediatrics*.

**Appendix C:**

Dawood, G., Klop, D., Pillay, M., & Grimmer, K. (submitted: 17 October 2019). Auditory processing and learning capacity in 9 to 12-year-old children from Cape Town, South Africa: A cross-sectional study. *PLOS ONE*

### Objective 1. Hearing profile of CLHIV and CNLHIV

The first objective was to describe the hearing profile of CLHIV and CNLHIV.

#### *Pure Tone Audiometry*

**Failed Tests.** The percentage of children who failed each frequency tested is described in Table 3, for CLHIV and CNLHIV, and the difference between CLHIV and CNLHIV is reported as p values from  $\chi^2$  tests. For each test, the same threshold pass/fail was set, but this differed between CLHIV and CNLHIV because of test circumstances. For CLHIV, the fail threshold was >15dBHL, whilst for CNLHIV it was >25dBHL.

**Table 3:** *Pure Tone Audiometry - Fail Results per Frequency*

Frequency Ear	CLHIV	CNLHIV	Significance
250Hz Right	0%	6.3%	0.21
250Hz Left	25%	6.3%	0.05
500Hz Right	29.2%	6.3%	0.02*
500Hz Left	16.7%	6.3%	0.21
1000Hz Right	29.2%	3.1%	0.005*
1000Hz Left	16.7%	9.4%	0.41
2000Hz Right	20.8%	0%	0.01*
2000Hz Left	12.5%	0%	0.05
4000Hz Right	16.7%	6.3%	0.21
4000Hz Left	16.7%	6.3%	0.21
8000Hz Right	29.2%	6.3%	0.03*
8000Hz Left	29.2%	9.4%	0.06

**Hearing Loss.** Eleven children overall (19.6% sample) were diagnosed with hearing loss (Yes/No), with seven recording it in both ears (63.6% of those with hearing loss).

However, there were significantly more CLHIV with hearing loss in both ears (N=6 (25%)) than CNLHIV (N=1 (3.1%)). In children with hearing loss, there were eight CLHIV (66.7%) and four CNLHIV (33.3%) who reported hearing loss in either or both ears.

In the eight CLHIV with hearing loss in one or both ears (34.8% total CLHIV), there were 14 ears with hearing loss. Six participants had bilateral hearing loss, and the remaining two participants had unilateral hearing loss. In both cases of unilateral hearing loss, the right ear was affected. In the 14 involved ears, nine ears (64.2%) presented with conductive hearing loss and five ears presented with sensorineural hearing loss.

The mean PTA-Right was 15.2 (12.7), and PTA-Left was 12.6 (9.9). The mean overall severity score of hearing loss in the left ear was 0.4 (SD 0.8), and in the right ear, it was 0.6 (SD 0.9). For hearing loss in both ears, the severity score was 1.0 (SD 1.7).

**ART and Hearing Loss.** Hearing loss in one or both ears was significantly associated with low lifetime exposure to ART (3.7 (95%CI 1.0-14.5)).

**Type of Hearing Loss.** Hearing loss was determined as conductive, sensorineural, or unspecified (where bone conduction testing was not done). Table 4 reports on the type of hearing loss experienced by CLHIV and CNLHIV per ear.

**Table 4:** *Type of Hearing Loss*

Type of hearing loss Ear	CLHIV n (%)	CNLHIV n (%)	Significance
No hearing loss Right	16 (66.7%)	30 (93.7%)	<0.05*
No hearing loss Left	18 (75.0%)	29 (90.6%)	<0.05*
Conductive hearing loss Right	4 (16.7%)	0 (0%)	<0.05*
Conductive hearing loss Left	4 (16.7%)	0 (0%)	<0.05*
Sensorineural hearing loss Right	2 (8.3%)	0 (0%)	>0.05
Sensorineural hearing loss Left	1 (4.2%)	0 (0%)	>0.05
Unspecified hearing loss Right	2 (8.3%)	2 (6.3%)	>0.05
Unspecified hearing loss Left	1 (4.2%)	3 (9.4%)	>0.05
Significant difference Right	0.04*		
Significant difference Left	0.06*		

**The Severity of Hearing Loss.** Considering the entire sample (children with, and without hearing loss), the overall severity of hearing loss score for either ear ranged from 0-3 (mean 0.3, SD 0.7), and the overall both-ear score ranged from 0-6 (mean 0.6, SD 1.4). Among only those children with hearing loss (all with severity ranges from 1-3), for children with Right ear loss only, the severity score was 2.1 (SD 0.9), and for children with Left ear loss only, the severity score was 1.6 (SD 1.1). The overall severity score for the seven children with hearing loss in both ears was 3.7 (SD 1.8). The mean severity of hearing loss scores (SD) for CLHIV and CNLHIV is reported in Table 5, along with significant differences between scores.

**Table 5:** *Severity of Hearing Loss – Mean (SD)*

Ear	CLHIV	CNLHIV	Significance
Severity Right	1.8 (0.9)	3.0 (0)	0.09
Severity Left	1.5 (0.8)	3.0 (0)	0.05
Severity both ears	3.3 (1.6)	6.0 (0)	0.2

***Electroacoustic Measures*****Table 6:** *Types of Tympanograms*

Tympanogram	CLHIV n (%)	CNLHIV n (%)	Significance
<i>Right ear</i>			
A	18 (75%)	25 (83.3%)	>0.05
As	2 (8.3%)	3 (10%)	
B	2 (8.3%)	1 (3.3%)	
C	2 (8.3%)	1 (3.3%)	
<i>Left ear</i>			
A	18 (75%)	28 (93.3%)	>0.05
As	2 (8.3%)	0 (0)	
B	2 (8.3%)	1 (3.3%)	
C	2 (8.3%)	1 (3.3%)	

**Tympanometry.** There was no significant difference between the tympanograms obtained for the CLHIV compared to CNLHIV. Tympanometry results are reported in Table 6.

**OAE.** Only the CLHIV were tested, as the equipment was only available at the tertiary hospital. Moreover, only 29% of CLHIV could be tested. This was due to various reasons, including children refusing to be tested, high levels of ambient noise, and equipment not being available or faulty on the day of testing. In those who could be assessed, “Refer”



results were recorded in the Right ear for two of the 15 CLHIV (13.3%) and in the left ear for three of the CLHIV (18.8%).

**Acoustic Reflex Testing.** For all *ipsilateral reflex* tests, data were missing on five CLHIV children. At 500Hz for the Right and Left ears, significantly more CLHIV than CNLHIV children had present reflexes (Right ear N=19 (90.5%); N=17 (56.7%) respectively) ( $p<0.05$ ); Left ear N=20 (95.2%); N=13 (43.2%) respectively) ( $p<0.05$ ). However, this was not the case at 1000Hz (Right ear CLHIV N=19 (90.5%); N=17 CNLHIV (56.7%) respectively) ( $p<0.05$ ); Left ear N=20 (95.2%); N=13 (43.2%) respectively) ( $p<0.05$ ); and at 2000Hz (Right ear CLHIV N=17 (80.9%); CNLHIV N=20 (66.7%) respectively) ( $p<0.05$ ); Left ear CLHIV N=20 (95.2%); CNLHIV N=15 (50.0%) respectively) ( $p<0.05$ )).

For all *contralateral reflex* tests, the data is reported only for CLHIV because the equipment was not available for testing in schools. Right contralateral acoustic reflex thresholds were present at 500Hz for 18 of 20 children tested (90.0%), 1000Hz for all 20 children (100%) and 2000Hz for 19 of 20 children tested (95.0%). Left contralateral responses were present at 500Hz for 19 of 20 children (95.0%), 1000Hz for 19 of 20 (95.0%) and 2000Hz for 18 of 20 children (90.0%).

## **Objective 2.** Auditory processing capacities in CLHIV and CNLHIV

The second objective of the study was to describe auditory processing capacities in CLHIV and CNLHIV

This section reports auditory processing in two ways; firstly, as four individual measures, and secondly as a combined measure. It is not usual practice to report a combined measure for discrete skills, however, there is no agreement on the best way of reporting auditory processing. As auditory processing is an area that required significantly more research investment, the researcher is of the opinion that providing two different ways of

understanding the data will be helpful for future researchers. The use of factor weighting, albeit on a small sample provides a better indication of the relative importance of the individual components than simply combining binary (1,0) forms of each measure into a composite score. Providing the data in two separate ways gives readers the opportunity to consider individual auditory processing measures or one composite measure.

Auditory processing capacities were assessed only in children with no hearing loss (N=44 [16 CLHIV, 28 CNLHIV]). However, not all the children were able to complete all auditory processing measures (Table 7).

**Table 7:** *Auditory Processing Capacities*

Measure	Mean (SD)	Range (Percentile)	N meeting pass criteria (%)
GD			22 (50)
AFG	6.7 (9.1)	0.1-50	2 (4.6)
CWFR	14.6 (19.3)	0.1-63	13 (29.5)
WD	42 (23.2)	2-84	

**Table 8:** *Auditory Processing Capacity - Gender, HIV-status, Home Language ( $p < 0.05$ )*

Measure	Gender	HIV status	Home language
GD	0.79	0.24	0.40
AFG	0.02*	0.06	0.09
CWFR	0.06	0.01*	0.37
WD	0.51	0.96	0.29

### ***Gap Detection***

Of the 22 who met the pass criteria, N=5 (33.3%) CLHIV and N=17 (60.7%) CNLHIV (trend towards a significant difference in case-control proportions) ( $p=0.06$ ) met the pass criteria (Keith, 2009a).

### ***Auditory Figure-Ground 8+***

Of the 2 who met the pass criteria N=0 (0%) CLHIV and N=2 (7.1%) CNLHIV (no significant difference in case-control proportions) met the pass criteria (Keith, 2009a). Applying a descriptive rating to the AFG results (Keith, 2009b), for CLHIV, one participant (6.3%) was rated as normal, N=11 (68.8%) were disordered, and N=4 (25%) were borderline, while for CNLHIV children, N=8 (28.6%) were rated as normal, N=7 (25%) were disordered, and N=13 (46.4%) were borderline. Considering the mean standardized AFG scores, the CLHIV had significantly lower mean scores (2.8 (SD 1.9)) than CNLHIV (5.2 (SD 2.2)) ( $p<0.05$ ). The same significant finding occurred for the percentile scores (CLHIV mean 2.4 (SD 4.3), CNLHIV mean 9.6 (SD 10.2)  $p<0.05$ ). When considering ear advantage ratings (typical and atypical) for the AFG, there was no significant difference between CLHIV and CNLHIV scores. For CLHIV, 11 of 16 participants tested were atypical (68.7%), and for CNLHIV, 17 of 28 participants tested were atypical (60.7%) ( $p>0.05$ ).

### ***Competing Words- Free Recall***

Significantly fewer CLHIV N=2 (12.5%) met the pass criteria (Keith, 2009a), compared with CNLHIV (N=11 (39.3%)) ( $p<0.05$ ). Applying a three-level rating to CWFR scores (Keith, 2009a), for CLHIV, three participants (18.8%) were rated as normal, N=7 (43.8%) were disordered, and N=6 (37.5%) were borderline, while for CNLHIV, N=13 (36.4%) were rated as normal, N=6 (21.4%) were disordered, and N=9 (32.1%) were borderline. There were no significant differences between these percentages. Considering the

mean standardized CWFR scores, the CLHIV had significantly lower mean scores (4.1 (SD 2.3)) than CNLHIV (6.4 (SD 3.1)) ( $p < 0.05$ ). The same significant finding occurred for the mean CWFR percentile scores (CLHIV mean 6.3 (SD 10.6), CNLHIV mean 20.4 (SD 21.7) ( $p < 0.05$ )). Similar to the finding for AFG, when considering ear advantage ratings for the CWFR, there was no significant difference between CLHIV and CNLHIV percentage mean scores (CLHIV mean 8.0 (SD 4.5); CNLHIV mean 7.3 (SD 5.4)). Supporting this finding, for CLHIV, five of 16 participants tested were considered to be atypical (31.2%), and for CNLHIV, 12 of 28 participants tested were atypical (42.9%) ( $p > 0.05$ ).

### ***Word Discrimination***

Mean word discrimination test differences between CLHIV and CNLHIV are reported in Table 9. There were no significant differences between CLHIV and CNLHIV for any test.

**Table 9:** *Word Discrimination - Mean (SD)*

	<b>CLHIV</b>	<b>CNLHIV</b>	<b>Significance</b>
Word discrimination rank scores	29.7 (2.2)	30.0 (1.6)	$>0.05$
Word discrimination standardized scores	9.3 (2.8)	9.2 (1.9)	$>0.05$
Word discrimination percentile scores	43.8 (28.7)	41.9 (20.9)	$>0.05$

**Objective 3.** Predictor variables associated with hearing loss in CLHIV

The third objective of the study was to investigate the predictor variables associated with hearing loss in CLHIV.

***Hearing Loss***

There were eight CLHIV (66.7%) who reported hearing loss in either or both ears (a non-significant difference of proportions within CLHIV), and there was a non-significant association between HIV and hearing loss (OR 3.7 (95%CI 0.8-14.5)). This finding persisted when further considering the severity of hearing loss. Compared with participants with no hearing loss (severity=0), the association between HIV status and minimal/ mild severity of hearing loss was OR 8.2 (95%CI 0.9-79.4), and for moderate/ high severity of hearing loss, the association with HIV status was OR 2.1 (95%CI 0.4-11.3).

**Factors Associated with Hearing Loss in CLHIV.** ART lifetime exposure, history of defaulting on ARV, WHO staging of HIV, viral load, disease history, prematurity, developmental delay, history of absence from school, history of repeating a grade, age-for-grade, family income, parent/caregiver status, and caregiver education were tested for associations with HL, using univariate logistic regression modelling. CD4 count was only available from the case-notes of 11 participants, precluding analysis of associations with HL. Table 10 reports the cut point for each variable, and the strength of association using odds ratios (95%CI). Only ART lifetime exposure less than the median (80.6%) provided evidence of an essential association with hearing loss.

**Table 10:** *Association between Hearing Loss (either ear) and Predictor Variables*

Variable	Cut-off point	Odds ratio (95%CI)
ART lifetime exposure	<75%	4.4 (1.1-18.5) *
History of defaulting on ARV	Yes	1.0 (0.2-7.4)
WHO staging	Stages 3 or 4	1.9 (0.5-7.9)
Viral load	LDL	1.7 (0.3-9.1)
Disease history	TB, malaria, meningitis	2.6 (0.7-11.5)
Prematurity	<38 weeks gestation	0.6 (0.2-3.7)
Developmental delay	Any	1.7 (0.1-36.7)
History of absence from school	Yes	0.4 (0.1-3.4)
History of repeating a grade	Yes	0.7 (0.2-3.6)
Age-for-grade	Grade 3 $\geq$ 10 years or Grade 4 $\geq$ 11 years or Grade 5 $\geq$ 12 years or 6 $\geq$ 13 years	2.6 (0.6-10.9)
Family income	< R28320 / year	1.7 (0.3-8.8)
Parent caregiver	No	1.6 (0.3-9.2)
Caregiver education	Completed Grade 10 or lower	0.4 (0.1-1.6)

**Objective 4.** Association between auditory functioning and learning capacities

The fourth objective was to test the association between auditory functioning (hearing and auditory processing) and learning capacities (NVIQ, STM and WM) in the CLHIV and CNLHIV. Before the results can be presented relative to the objective, results pertaining to NVIQ, STM, and WM are presented.

All children (N=55) were assessed for NVIQ (irrespective of hearing loss).

**Table 11:** *Learning Capacity - Mean (SD)*

Measure	Mean (SD)	Range
NMF	39.1 (27.1)	1-98
NMR	27.4 (24.2)	1-90
TONI	32.0 (17.6)	6-84

The mean TONI 4 percent score was 32 (SD 17.6), ranging from 6-84. (Table 11)

*STM, WM, and NVIQ.* Number memory forward, number memory reversed, and TONI 4 scores, each considered as rank, standardized and percentile mean scores, and an overall TONI 4 score reported as an integer (average or above average, and below-average). All children (irrespective of hearing loss) provided information on attributes using the TONI 4 score, which did not require intact hearing. Working memory, however, required intact hearing and thus could only be tested on such children.

CNLHIV had significantly higher TONI 4 percentile scores compared with CLHIV (39.9 (SD 17.9) compared with 21.4 (SD 10.1), respectively) ( $p < 0.05$ ). For CLHIV, 14 participants (58.3%) TONI 4 scores were rated as being below-average, which was significantly higher than for CNLHIV (5 children, 15.6%) ( $p < 0.05$ ). Using this measure, CLHIV were 7.6 times more likely (95%CI 2.2-26.5) to have below-average TONI 4 scores than CNLHIV. There were significant differences between CLHIV and CNLHIV for mean NMR ranked scores, and all the TONI 4 mean scores.

Table 12 reports mean scores for the integer learning capacities measures for CLHIV and CNLHIV, and significant differences between each measure.

**Table 12:** *Learning Capacity for CLHIV and CNLHIV - Mean (SD)*

Learning capacity score	CLHIV	CNLHIV	Significance
NMF ranked score	17.6 (4.3)	17.6 (4.2)	>0.05
NMF standardized scores	9.2 (2.8)	8.9 (2.8)	>0.05
NMF percentage scores	40.3 (28.6)	38.4 (26.7)	>0.05
NMR ranked score	8.0 (2.4)	9.7 (2.1)	<0.05*
NMR standardized scores	6.5 (2.3)	7.9 (2.2)	>0.05
NMR percentile scores	18.9 (23.1)	31.9 (23.9)	>0.05
TONI 4 ranked score	20.1 (4.3)	27.9 (5.8)	<0.05*
TONI 4 standardized score	87.3 (5.5)	95.8 (7.8)	<0.05*
TONI 4 percentile score	21.4 (10.1)	39.9 (17.9)	<0.05*

***Determining Latent Composite Learning Capacities***

In children with no hearing deficits, factor analysis was employed to identify the latent variable underpinned by the inter-relationships between the three learning capacities. One factor was identified with the NMR ranked percent weighting = 0.82; NMF ranked percent weighting = 0.57; and TONI 4 ranked percent weighting = 0.60. The mean per-child overall latent learning capacity score was 1.17 (SD 0.8); (range 0 to 1.99) by applying these factor weightings to the per-child test scores. There was a significant difference between CLHIV and CNLHIV mean scores (case mean 1.51 (SD 0.58); control mean 0.92 (SD 0.68)) ( $p < 0.05$ ).



**Table 13:** *Learning Capacity - Gender, HIV-status and Home Language ( $p < 0.05$ )*

Measure	Gender	HIV status	Home language
NMF	0.97	0.82	0.22
NMR	0.27	0.09	0.46
TONI 4	0.32	0.001*	0.009*

**Demographics as a Predictor of HIV.** Gender was not associated with HIV status (OR 0.7, 95%CI 0.2-1.9) (Table 13).

**Demographics as a Predictor of Learning Capacity.** There was no influence of gender on NVIQ (TONI 4 percentile scores (females mean 33.0 (SD 18.1) and males (36.1 (SD 21.2 (F value 0.4 (df=1)  $p > 0.05$ )). There was a significant effect of speaking English at home on language performance scores (mean TONI 4 percentile rank score 47.7 (SD 21.0), compared with Afrikaans language (mean 28.8 SD 14.1) and African languages (mean 27.5, SD 18.3) (F value 8.3 (df=2)  $p < 0.01$ )). There were similar significant findings for languages spoken at school, with English school-language TONI 4 percentile rank scores being significantly higher than for the other school languages (English mean TONI 4 score 42.8 (SD 21.0), Afrikaans mean 28.6 (SD 13.9) and African languages mean 14.8 (SD 8.7) (F value 8.1 (df=2)  $p < 0.01$ )). Moreover, there was no influence of experiencing a difference in languages spoken at home and school on TONI 4 percentile rank scores (the same language mean 34.7% (SD 20.3%), different language mean 33.5% (SD 17.9%) (F value 0.04 (df=1)  $p > 0.05$ )).

**HIV as a Predictor of Hearing Loss and NVIQ.** NVIQ was significantly different between HIV groups, with the CNLHIV having a significantly higher TONI 4 score (mean 39.5%, SD 18.5%) compared with CLHIV (mean TONI 4 score (21.4% (SD 10.1%)). Using

the median division in TONI 4 scores (30%), HIV status was significantly associated with the risk of low TONI 4 scores (OR 15.4 (95%CI 3.7-63.8)) (Table 13).

**Hearing Loss and NVIQ.** The association between hearing loss and NVIQ was considered in two ways, with neither demonstrating a significant association. There was a minimal association ( $r^2=1.0\%$ ,  $p>0.05$ ) when using both hearing loss and learning NVIQ as integer variables in a linear regression model. There was no significant association for one ear (either Left or Right) OR 0.8 (95%CL 0.1-6.2), or both ears affected OR 1.3 (95%CI 0.1-15.7)) when using categories of hearing loss of none (default comparator), one ear or both ears, and testing against learning capacity divided at the median value. There were insufficient numbers of children with mild-moderate hearing loss to resolve a logistic regression model, which considered three independent levels of hearing loss severity (none (default), mild-moderate, or severe). Thus, a binary form of hearing loss severity data was developed, as none, or combined categories of mild, moderate, and severe. There was no association between NVIQ and hearing loss categories (OR 3.5 (95%CI 0.9-13.5)).

**Multivariate Analysis.** The only significant potential confounder that could be applied to the multivariate model of HIV status (exposure) and NVIQ (outcome) was hearing loss severity. The crude and adjusted model outputs are reported in Table 14. The overall variance of the crude model (-2 Log L) was 87.3. The amount of variance explained by adjusting this model by hearing loss severity was not significant (less than the threshold significant chi-square value of 5.99 (df=2)).

**Table 14:** *Association between HIV and NVIQ - Multivariate Analysis*

Primary exposure	Potential confounder	OR (95%CI)	Likelihood Ratio	df	Chi <sup>2</sup> change	Critical chi <sup>2</sup> value for df	Sig of change
HIV+		(crude) 15.4 (3.7-63.8)	19.9	1		3.8	p<0.05
	Hearing loss severity	(adjusted) 21.1 (4.1-109.5)	20.4	2	0.5	5.9	p>0.05

**Sample Descriptors.** This research examined data of the 43 participants with no hearing loss (78.2% sample). There were 15 CLHIV (34.9% sample), of whom 8 (53.3%) were female, and 28 CNLHIV (65.1%), of whom 15 were female (53.3%).

Overall, 30.2% of participants spoke English, 41.9% spoke Afrikaans, and the remainder (27.9%) spoke an African language. There was a significant difference ( $p<0.05$ ) in the frequency of speaking a primary home language for CLHIV and CNLHIV, with 92% CNLHIV primarily speaking English, but only 7.7% CLHIV; 61.1% CNLHIV primarily speaking Afrikaans but only 38.9% CLHIV; and 41.7% CNLHIV primarily speaking an African language compared with 58.3% CLHIV. There was a difference in primary language spoken at school, between CLHIV and CNLHIV that trended towards significance ( $p=0.07$ ), with 80% CNLHIV speaking English at school compared with 20% CLHIV; 57.9% CNLHIV speaking Afrikaans compared with 42.1% CLHIV; and 25% CNLHIV speaking an African language compared with 75% CLHIV. Overall, approximately 1:5 participants (20.9%) spoke a different language at home and school, reflecting 14.3% CNLHIV and 33.3% CLHIV ( $p>0.05$ ). No English-speaking children reported a difference between home and school language; however, home-school language difference was found in five CLHIV (one

Afrikaans-speaker (20%), and four African language speakers (80.0%); and in four African speaking CNLHIV (100%).

Of the 14 CLHIV on whom information on ART was available from hospital records, the mean percentage of lifetime exposure to ART was 73.4% (21.5%).

**NVIQ and WM.** CNLHIV with no HL had significantly higher TONI 4 and NMR percentile scores compared with CLHIV with no HL, but there was no difference in mean percentile scores for NMF between CLHIV and CNLHIV (Table 15).

**Table 15:** *NVIQ, STM and WM - Mean (SD)*

	CLHIV (n=15)	CNLHIV (n=28)	P-value ANOVA models
TONI 4 percentile ranks	20.4 (10.1)	40.6 (19.2)	<0.05*
Number memory forward (NMF) ranks	37.8 (27.1)	38.4 (26.7)	>0.05
Number memory backward (NMR) ranks	11.2 (11.9)	31.9 (23.9)	<0.05*

**Factor Analysis.** Latent ‘composite learning capacity’ was explained by one factor, which included all three learning capacities (NMR ranked percent weighting = 0.79; NMF ranked percent weighting = 0.62; TONI 4 ranked percent weighting = 0.71). The mean per-child overall latent learning capacity score was 1.2 (SD 0.7; range 0 to 2.1), with a significant difference between CLHIV and CNLHIV (mean CLHIV 1.6 (SD 0.5); mean CNLHIV 0.9 (SD 0.7) ( $p < 0.05$ )).

**Table 16:** *Auditory Processing and Learning Capacities for Participants with Normal Hearing - Linear Measures of Association*

Means	CLHIV (n=15)	CNLHIV(n=28)	p-value (ANOVA models)
AFG%	2.2 (4.2)	9.5 (10.2)	0.007*
CWFR%	5.9 (10.4)	20.4 (21.7)	0.01*
WD%	43.8 (28.7)	40.1 (21.4)	0.63
NMF%	39.0 (27.4)	40.3 (26.5)	0.89
NMR%	15.3 (15.1)	31.9 (23.9)	0.03*
TONI 4 %	21.3 (9.8)	40.1 (19.7)	0.007*
Linear measures of association ( $r^2$ )	<i>With TONI 4 %</i>		
AFG%	0.113 (11.3%)*		
CWFR%	0.177 (17.7%)*		
WD%	0.02		
	<i>With NMF%</i>		
AFG%	0.002		
CWFR%	0.001		
WD%	0.02		
TONI 4 %	0.02		
	<i>With NMR%</i>		
AFG%	0.104 (10.4%)*		
CWFR%	0.04		
WD%	0.01		
TONI 4 %	0.116 (11.6%)*		

**Auditory Processing.** Twenty-one participants of the sample (48.8%) presented with poor auditory processing scores, comprising 11 CLHIV and 10 CNLHIV (52.4%, 47.6%, respectively). CLHIV incurred a significantly higher risk of having poor auditory processing scores compared with CNLHIV (OR 4.95 (95%CI 1.24-19.69). Not surprisingly, the mean percentile scores for each of the auditory processing tests (AFG, CWFR, WD) was generally

lower for CLHIV than CNLHIV (Table 16). There was modest evidence of an association between GD and HIV (OR 3.3 (95%CI 0.9-11.6)).

**Auditory Processing Capacities and Learning Capacities.** Significant associations were found between the TONI 4 percentile rank score and the percentile rank scores for two auditory processing tests, namely AFG and CWFR. Significant associations were also found between NMR and AFG, as well as between NMR and TONI 4. NMF was not significantly associated with any auditory processing capacities or with TONI 4 (Table 16).

**Factor Analysis.** There were two latent variables derived from the factor analysis (explaining 58% and 42% respectively, of the total variance). The factor explaining the largest percentage of variance included variables of AFG (weighting = 0.91); CWFR (weighting= 0.83); WD (weighting = 0.39); and laterality (weighting = 0.36). The second factor contained only one variable, GD (weighting = 0.75). The mean per-case score for the first latent variable was 0.50 (0.36) while for controls, it was 0.29 (0.37). For the second latent variable, the per-CLHIV mean score was 1.74 (0.71) whilst for CNLHIV it was 0.96 (0.82)).

**Univariate association between composite auditory processing capacity and learning capacity scores.** There was a significant and moderately strong linear association between the continuous forms of these two latent variables without taking account of CLHIV or CNLHIV ( $r^2=19.4\%$  ( $p<0.01$ )). However, when considering these variables in binary form, the crude association was non-significant (Odds Ratio (OR) 2.8 (95% Confidence Interval (CI) 0.8-9.4) (Likelihood Ratio 2.8 ( $p<0.05$ )).

**Influence of Predictor Variables.** Only HIV status produced significantly different means when considering outcomes of composite auditory processing and learning capacity scores (Table 17). The CLHIV produced significantly higher scores than the CNLHIV

(meaning that CLHIV accumulated more poor scores in the component auditory processing and learning capacity composite measures). Gender, language spoken at home, and differences between home and school language did not influence the mean composite auditory processing or the learning capacity composite measures.

**Table 17:** *Auditory Processing and Learning Capacities - Composite Scores*

		<b>Auditory processing composite means (SD)</b>	<b>p-value</b>	<b>Learning capacity composite means (SD)</b>	<b>p-value</b>
Gender (degrees of freedom (df) =1)	Female	1.8 (0.9)	0.05	1.1 (0.6)	0.4
	Male	1.3 (0.9)		0.9 (0.8)	
Language at home (df=2)	English	1.1 (0.8)	0.05	0.7 (0.6)	0.05
	Afrikaans	1.8 (0.9)		1.2 (0.6)	
	African language	1.8 (0.8)		1.3 (0.7)	
	Difference between primary home and school language (df=1)	1.6 (0.9)	0.8	1.1 (0.7)	0.7
HIV status (df=1)	Difference	1.5 (0.8)		0.9 (0.5)	
	CNLHIV	1.2 (0.8)	<0.001*	0.8 (0.7)	<0.001*
	CLHIV	2.2 (0.8)		1.5 (0.6)	

### **Association between Composite Learning Capacity and Composite Auditory**

**Processing Variables.** The Crude Odds Ratio (COR) for the association between the auditory processing and learning capacity composite measures (split at the median) was non-significant (2.7 (95%CI 0.8-9.5)). Adjusting this by HIV status, the adjusted OR (AOR) was significantly lower than the COR (1.8 (95%CI 0.5-7.5)), supported by a significant change in

the Likelihood ratio (6.6 (df=2)  $p < 0.05$ ). The AOR was also non-significant. The wide confidence intervals potentially reflected the impact of small numbers in some cells.

**Lifetime Exposure to ART.** There was some indication in the CLHIV that the extent of exposure to ARV influenced auditory processing and learning capacity, in particular in the NMF measure. Table 18 outlines the differences between CLHIV, whose lifetime exposure was less than 75% (N=7), compared with those whose exposure was longer (N=8). There was a non-significant association between gap detection and ARV lifetime exposure (OR 0.67 (95% CI 0.08 – 5.87).

**Table 18:** *Auditory Processing Capacity, Learning Capacity and ARV Lifetime Exposure*

	<75% LT exposure	>75% LT exposure	p value
TONI 4 ranked percent	21.25 (11.54)	19.42 (9.09)	>0.05
NMF ranked percent	24.25 (18.12)	55.83 (27.78)	<0.05*
NMR ranked percent	14.71 (14.02)	6.20 (6.26)	>0.05
AFG ranked percent	2.47 (5.51)	2.42 (3.39)	>0.05
CWFR ranked percent	4.42 (8.33)	9.21 (13.47)	>0.05
WD ranked percent	48.14 (25.96)	36.71 (33.30)	>0.05



## Summary of Results

- Hearing loss was found in CLHIV, despite being on HAART, and having a median lifetime ART exposure above 75% at some time during their lifetime.
- Hearing loss was also found in CNLHIV.
- Being HIV positive was significantly associated with compromised learning capacities and auditory processing capacities in children aged 9 to 12 years, but not with hearing loss.

## Chapter 7

### Case Studies

This chapter is a stand-alone chapter which aims to provide insights into the complexity of factors associated with children's capacity to learn, by providing case studies that explore the subtlety of differences between CLHIV and CNLHIV in the same socio-economic demographic.

### Background

Chapter Two described the complexity of HIV in South Africa, particularly for the next generation, who, on the one hand, may be protected from opportunistic infection by ART, but on the other hand, may suffer consequences of being on ART that is yet to be fully understood. Chapter One highlighted the complex causal pathway in which HIV is potentially related to subsequent deficits in auditory functioning, and children's potential to optimize learning capacity. Educators in schools in low socio-economic areas in South Africa often deal with large classes, and they may not have the time to understand the learning needs of each student (Spaull, 2013). There are emergent concerns regarding how children process information auditorily while hearing loss appears to be on the decline. Teachers confronted by a child, whose health status may or may not be known to them, and who has difficulty learning, may not have the skills or the time to ensure that the child is supported adequately to optimise learning. Screening for hearing loss does not provide a full picture of impediments to how children learn, particularly in low socio-economic areas where parents may not have the money or knowledge to seek help for their child who has fallen behind at school. Anecdotally, there is so much pressure on teachers within the school system (i.e., large classes, inadequate resources) that children with educational deficits, which are

underpinned by subtle health and developmental issues, may not receive the attention that they require.

## Methods

### *Study Design*

This chapter describes four case-control dyads, matched as closely as possible by age, gender and hearing loss, and four case-case dyads, matched for age and gender, whose differences were hearing loss (one case with intact hearing, and the other with hearing loss). These comparisons were undertaken to provide insights into how these children might present in class.

### *Process of Matching*

**Case-Control Dyad.** Cases were identified, with and without hearing loss, and matched controls were then sought. Matching cases and controls for the extent of hearing loss was difficult; however, because of the eight cases with hearing loss, six had hearing loss in both ears, while of the four controls with hearing loss, only one had hearing loss in both ears. The case-control dyads are listed in Table 19.

**Table 19:** *Case-Control Dyads - Age, Gender and Hearing Loss*

Cases				Control			
<i>ID</i>	<i>Age</i>	<i>Gender</i>	<i>Hearing loss</i>	<i>ID</i>	<i>Age</i>	<i>Gender</i>	<i>Hearing loss</i>
72	10.1	Female	None	489	10.8	Female	none
399	10.2	Male	None	56	10.0	Male	none
353	11.7	Female	Yes (one ear)	392	12.6	Female	Yes (one ear)
6	10.4	Male	Yes (two ears)	184	11.5	Male	Yes (one ear)

**Case-Case Dyad.** Cases were identified, with and without hearing loss, and matched for age and gender. It was easier to match cases with no hearing loss, with cases with hearing loss, because there were more cases with hearing loss in both ears. Table 20 lists the case with normal hearing and case with hearing loss dyads.

**Table 20:** *Case-Case Dyads - Age, Gender and Hearing Loss*

Case with normal hearing			Case with hearing loss			Extent of hearing loss
<i>ID</i>	<i>Age</i>	<i>Gender</i>	<i>ID</i>	<i>Age</i>	<i>Gender</i>	
138	9.2	Male	295	9.2	Male	Both ears
72	10.1	Female	456	10.2	Female	Both ears
62	10.8.7	Male	6	10.4	Male	Both ears
94	12.4	Female	40	12.5	Female	Both ears

**Reporting Standard.** The case report followed the CARE reporting standards where possible (Gagnier et al., 2013). However, much of the background, methods, and results were reported in earlier chapters; thus, this chapter focuses on individual results and how children may present in class.

**Measures of Outcome.** Three measures are reported in this chapter. Auditory processing is reported using the total factor score (as described in Chapter 5). Not every child in the dyads had auditory processing information, as intact hearing was required before undertaking these tests. The total factor score was derived from summing the number of deficits for each child for each auditory processing test, from the sum of two factors, derived from weighted variables. Factor 1 consisted of weighted GD only, and Factor 2 consisted of the sum of weighted AFG, CWFR, WD, and lateralization. Children scored 1 for each test

element if they scored below the expected median value (poor score). Higher factor scores thus reflected poorer auditory processing.

Similarly, the factor scores for the capacity to learn were reported, where higher scores also indicated poorer capacity to learn. Only one factor was required, including TONI 4, NMF, and NMR. The only common test across all children was the TONI 4 (which did not require intact hearing) because children with hearing deficits could not be tested for NMF and NMR. This measure of learning capacity is consequently also reported separately to the overall learning capacity factor score. For TONI 4, higher scores mean better performance.

For comparison purposes, the individual case scores are compared with the 95% confidence intervals of these measures. This information is provided below.

Mean (95%CI) AP total factor for all children with intact hearing: cases 1.3 (0.9-1.6); controls 2.2 (1.7-2.7).

TONI 4 percentile for all children: cases 21.2 (95%CI 7.9-14.5); controls 39.9 (95%CI 14.4-23.9).

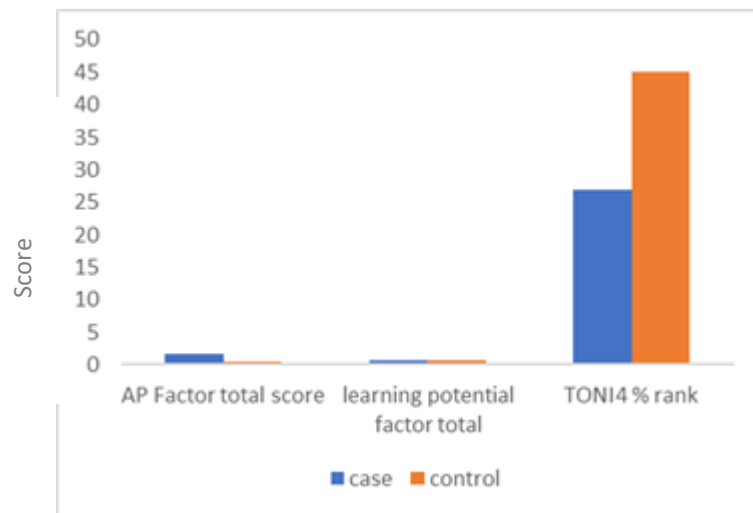
- For children with no hearing loss: cases 20.4 (95%CI 14.8-26.0); controls 40.6 (95%CI 33.1-48.0).
- For children with hearing loss: cases 22.6 (95%CI 13.4-31.9); controls 35.7 (95%CI 29.5-42.0).

## Results

### *Case-Control Dyad 1: 72 (Case) / 489 (Control)*

This dyad described two ten-year-old females, both with intact hearing. The case had commenced ART when she was 4.4 years old (56.4% lifetime exposure to ART). Both children spoke Afrikaans at home and at school. The case had factor scores for auditory processing almost five times higher than the control (4.6 times higher); however, their capacity to learn factor scores did not differ significantly (0.71 and 0.61 respectively). Lower factor scores indicated good performance. The control had a TONI 4 percentile rank score nearly twice (1.7 times higher) that of the case, which indicated significantly higher non-verbal intelligence. Information on family circumstances and child history was available only for the case.

**Reflection.** This case-control dyad reflects a typical scenario that might confront a Grade 3 teacher. The CLHIV would present similarly in class to her peer who is HIV negative, in that her hearing is unaffected, and she is an appropriate age for her grade. Her capacity to process auditory information is significantly impaired; however, this is not reflected in the overall measures of her capacity to learn (NVIQ, STM, and WM). This suggests that she has perhaps developed her memory to compensate for auditory processing difficulties, and the impact on her nonverbal capacity to learn only becomes apparent when the TONI 4 score is considered on its own. As this study is cross-sectional, it is not possible to determine the sequence of development of compensatory mechanisms. However, from a teacher's perspective, this child may not be flagged as having learning difficulties because she can repeat information even though she may not comprehend.



**Figure 6. Auditory Processing Capacity, Learning Capacity and NVIQ (Dyad 1)**

#### ***Case-Control Dyad 2: 353 (Case)/ 392 (Control)***

This female case-control dyad was aged 11.7 years (case) and 12.6 years (control), respectively. They were both classified as being from the same population group (coloured), and both had hearing loss in one ear. They were both in Grade 6, and neither had repeated a grade. They both spoke Afrikaans at home, but the case spoke Afrikaans at school, and the control spoke English. The case's TONI 4 percentile rank score was 30, compared with the control TONI 4 score of 39 (this being 1.3 times higher than the case). Their TONI 4 scores were both within the 95<sup>th</sup>% for cases and controls with hearing deficits, respectively. The case had commenced ART at age 2.3 years and has a history of TB or malaria. She was currently taking the following ARVS: Lamivudine, Abacavir, and Efavirenz, and she had never defaulted on her ART. Her CD4 count was 1494, and she had been initially classified as WHO stage 3. Information was available only on the case home circumstances. She was

being cared for by a single parent, who was employed, and whose family income was R12600 per year.

**Reflections.** The classroom ramifications for these females, of having a unilateral hearing loss, is that both would have some difficulty in a noisy classroom environment and learning may be compromised due to both children missing acoustic information, as well as being fatigued from having to listen with only one ear (Kuppler et al., 2013). Their capacity to learn was within expected limits for their peers (cases and controls), although the control had a 33% better score for the capacity to learn than the case. Although the case presents with many factors that are related to poorer neurocognitive skills, such as a history of TB/Malaria (Hrapcak et al., 2016; Nakku et al., 2017), being classified as WHO Stage 3 at diagnosis (Iloh et al., 2017) and being on Efavirenz (Hammond et al., 2019), being schooled in her primary language may mitigate some of the academic risks (Ouane & Glanz, 2011) posed by the other factors, as she has not yet repeated a grade.

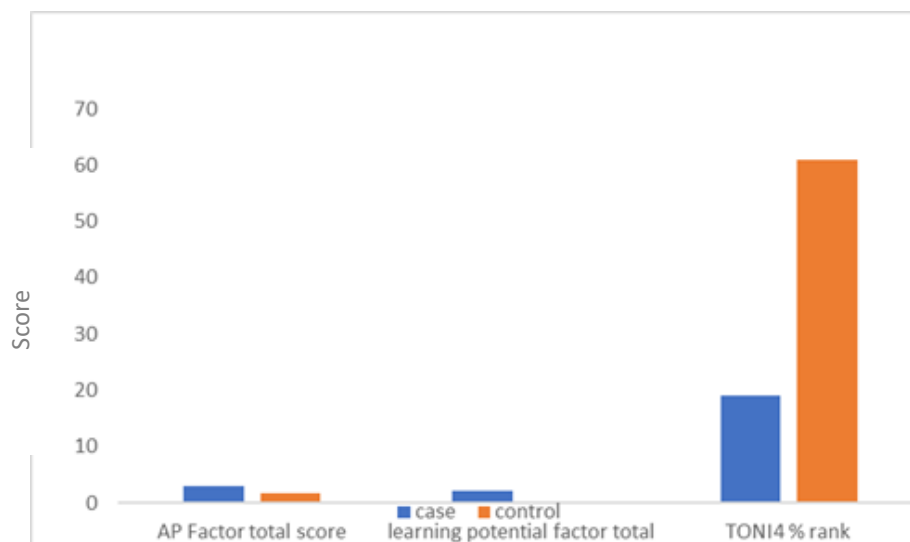
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### ***Case-Control Dyad 3: 399 (Case) / 56 (Control)***

These males were aged 10.2 years and 10.6 years, respectively. The case and control were classified as belonging to different population groups (coloured and white, respectively). Both spoke Afrikaans at school and home, and neither had hearing deficits. The case had commenced ART at birth and was taking Lamivudine, Abacavir, and Efavirenz. His CD4 count was 1600, and he had initially been diagnosed with WHO stage 1 HIV. The viral load was undetectable. He was being cared for by his married parents, and his mother had achieved Grade 7 schooling. The family income came from a pension (R28320 per year).



The case male had a total auditory processing factor score 1.6 times higher than the control, while his capacity to learn factor score was twice as high (the control having an uncompromised score of 0, while the case score was 2.1). This indicated difficulties with both auditory processing and the capacity to learn. The control's TONI 4 score was significantly higher by three times than the case score, indicating the significantly better capacity to learn. The case score fell within the expected 95% CI (range 14.8-26.0) while the control score exceeded the expected 95% CI range (33.1-48.0), indicating that this control was performing in the top 5% of the control group with no hearing loss.



**Figure 7. Auditory Processing Capacity, Learning Capacity and NVIQ (Dyad 3)**

**Reflection.** A teacher will experience these two males very differently. The case will struggle to follow and process information but will function similarly to other CLHIV; however, the control may perform better than his hearing peers. When one looks at the case's information, such as an initial WHO classification of Stage 3 (Iloh et al., 2017), using Efavirenz (Hammond et al., 2019) and lower socio-economic status (mother's grade and

family income) (Smith, 2011), these factors may be considered as flags for compromised neurocognitive skills.

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***Case Control Dyad 4: 6 (Case) / 184 (Control)***

These males were aged 10.4 years (case) and 11.5 years, respectively. Both belonged to the same population group (coloured), and both had hearing loss (the case in both ears and the control in one ear). In this case, they spoke a language other than English, Afrikaans, or isiXhosa at home but spoke isiXhosa at school, while the control spoke Afrikaans at both home and school. The case had commenced ART at birth and was currently taking Lamivudine, Abacavir, and Efavirenz. His CD4 count was 873, and he had a viral load of 1. He had not defaulted on ART during his lifetime. He was being cared for by a single parent, who had reached Grade 11 and was unemployed. The annual family income was R59616. He had a history of meningitis and TB / Malaria and was in Grade 3. He had previously repeated a grade.

The case's TONI 4 score was six compared to the control's score of 30. The case's score fell well below the 95%CI for cases with hearing loss (13.4-31.9) while the control score was within the 95%CI range (95%CI 29.5-42.0). The control score was five times higher than the case score.

**Reflection.** Teachers with these males in their class would find the case significantly impaired when it came to capacity to learn, compared with his peer who is HIV negative and has a unilateral hearing loss. Factors, although inter-related, that may be contributing to his poor academic performance (grade repetition), include HIV, hearing loss, and compromised

neurocognitive skills. Similar to some of the other cases, the male is taking Efavirenz (Hammond et al., 2019), has a history of meningitis (Rodenburg-Vlot et al., 2015) and is not being schooled in his primary language (Ouane & Glanz, 2011). All of these factors have been associated with compromised neurocognitive skills (Hammond et al., 2019). Furthermore, he has a history of TB/Malaria, which has also been associated with hearing loss in CLHIV (Hrapcak et al., 2016; Nakku et al., 2017).

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For the comparison between cases with normal hearing, and cases with hearing loss, only the TONI 4 percentage rank was appropriate, as all other tests required intact hearing (Auditory processing, Number Memory Forward and Back). All hearing-impaired cases in this section had hearing loss in both ears.

***Case-Case Dyad 1: 72 (Normal Hearing) / 456 (Hearing Loss)***

This case-case dyad reflected two ten-year-old females. Case 72 was already reported previously as part of a case-control dyad. Both cases spoke Afrikaans as a primary language at home, although case 456 spoke English at school. Both commenced ART late (4.4 years, five years respectively), and both were taking the following three ARVs: Lamivudine, Abacavir and Alluvia. Case 72 was reported to have defaulted on ART at some stage, although there was no information about the period when this happened. The hearing intact case (72) had a history of TB –? malaria. Both females were cared for by single parents. The case with hearing loss came from a relatively higher-income family (in this dataset) (R22360 per year) where the caring parent was employed. The comparison case family income was

R3360 per year (social grant), and the single parent was unemployed. There was no information regarding the parent's highest level of education. The case with hearing loss had repeated a grade and was currently in Grade 3, while the case with normal hearing was in Grade 4. The case with normal hearing had a TONI 4 percentile rank score of 29, which was 1.4 times higher compared with the case with hearing loss (score of 19). Both cases' TONI 4 percentile scores were within the respective 95%CI for cases.

**Reflection.** Although the HIV status of both these children may not be known to the teacher, the teacher would probably be aware that the case with hearing loss has academic issues since she has repeated a grade. The case with normal hearing had many factors (e.g., low socio-economic status) associated with poorer academic performance. However, the impact of these factors may have been mitigated by having normal hearing and being schooled in her primary language, which was not the situation for the case with hearing loss (Ouane & Glanz, 2011).

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#### ***Case-Case Dyad 2: 138 (Normal Hearing) / 295 (Hearing Loss)***

The second case-case dyad described two nine-year-old males. Both had been on ART since they were approximately three years old (2.9 years of age, 3.4 years of age, respectively). Both spoke Afrikaans at home and at school. The case with normal hearing obtained a TONI 4 percentile rank score of 19, compared with a score of 22 for the case with hearing loss. Both cases were in Grade 3, and neither had repeated a grade. The case with normal hearing had a history of meningitis, and both were on three ARVs (both were taking

Lamivudine and Alluvia, one was taking Abacavir, one was taking Zidovudine). Both had defaulted at some stage on their ART. The case with normal hearing had been designated at WHO stage 3 (indicating a more severe HIV state when initially diagnosed) while the case with hearing loss had been designated as WHO Stage 2. The case with hearing loss had a viral load of 2 and was being cared for by a single parent. No further information on social circumstances was available. The case with normal hearing had a viral load of 0, was being cared for by two parents, and the family income was R16200 per year (which came from a pension).

**Reflections.** As with the first case-case dyad, the teacher may not be aware of the cases' HIV status, nor of the implications of the disease. The case with normal hearing presented with more severe symptoms at diagnosis (WHO stage 3), as well as a history of meningitis, which has been associated with greater compromised neurocognitive skills (Iloh et al., 2017; Rodenburg-Vlot et al., 2015), perhaps explaining poorer TONI 4 scores. From a teacher's perspective, the child with normal hearing may not be considered to be at-risk for learning difficulties as compromised neurocognitive skills may be less evident than hearing loss. These cases were not able to be compared for auditory processing (which required intact hearing); however, the child with normal hearing had an auditory processing factor score (2.9) that was greater than the 95% percent confidence interval for his HIV peers with normal hearing (95% 1.8-2.6) and a capacity to learn score of 0.71, which was within the 95% confidence intervals for the same peer group. These results imply that the case with normal hearing is performing similarly, in terms of capacity to learn, to his HIV positive peers with normal hearing (95% CI 1.3-1.9). His poorer auditory processing score may be attributed to an immature auditory perceptual system, as variable performance on auditory processing tasks have been observed in children aged 6 to 11 years (Moore, Cowan, Riley, et al., 2011).

***Case-Case Dyad 3: 62 (Normal Hearing) / 6 (Hearing Loss)***

This case-case dyad describes two males aged 10.4 and 10.8 years, respectively. Case 6 had bilateral hearing loss, while case 62 had normal hearing. Both had started ART relatively young - at birth (case 6) and at two months of age (case 62). One spoke English at home and school, and the other spoke a language other than English, Afrikaans or isiXhosa at home but spoke isiXhosa at school. The case with hearing loss had a history of meningitis and TB/malaria, while the case with normal hearing had a history of attention deficit disorder. Neither had defaulted on their ART during their lifetime, and the case with hearing loss was currently taking Lamivudine, Abacavir, and Efavirenz, while the case with normal hearing was taking Lamivudine, Abacavir, and Alluvia. CD4 counts of 873 were recorded for the case with hearing loss and 608 for the case with normal hearing. The case with normal hearing had a classification of WHO Stage 2. Both cases were being cared for by single parents, who had reached grades 10 and 11, respectively. The parent of the case with normal hearing was employed, with an annual family salary of R24000. The family income of the case with hearing loss was R59616, even though this parent was unemployed.

There was a significant difference (more than four times) between TONI 4 scores for these two cases. The case with hearing loss had a score of 6 (which fell well below the 95%CI for cases with hearing loss (13.4-31.9)), while the case with normal hearing had a score of 27 (which exceeded the upper 95%CI (95%CI 14.8-26.0)).

**Reflections.** Teachers with these two cases in their class would notice the difference in their capacity to learn, specifically related to differences in hearing and significant differences in nonverbal intelligence (learning capacity). In this study, there was no association between hearing loss and capacity to learn, hence such a poor TONI 4 score was not expected. However, compromised neurocognitive skills have been observed in CLHIV

who are taking Efavirenz (Hammond et al., 2019) and in children who have had meningitis (Hudson, Viner, & Christie, 2013). Both possible factors may have affected the capacity to learn.

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***Case-Case Dyad 3: 94 (Normal Hearing) /40 (Hearing Loss)***

This case-case dyad described two females aged 12.3 years and 12.4 years, respectively. Case 40 presented with bilateral hearing loss. She had commenced ART at six months of age, while the case with normal hearing commenced ART at 16 months. The case with normal hearing spoke isiXhosa at home and English at school, while the case with hearing loss spoke Afrikaans at both home and school. The case with hearing loss had repeated a grade and was currently in Grade 6, while the case with normal hearing was in Grade 5. This suggests that the case with hearing loss may have commenced school earlier than the case with normal hearing.

The case with normal hearing had a TONI 4 percentile rank score of 10, which was lower than the lowest 95%CI for CLHIV with normal hearing (95%CI 14.8-26.0). The case with hearing loss had a TONI 4 percentile rank score of 30, which was within the 95%CI range for her HIV positive peers with hearing loss (13.4-31.9) although she had a history of TB (or Malaria). Both cases were taking Lamivudine and Abacavir, while the case with hearing loss was taking Alluvia, and the case with normal hearing was taking Efavirenz. Both cases had initially been classified as WHO stage 3, and the case with hearing loss had an undetectable viral load. The case with normal hearing had a CD4 count of 1077, but there was no information on CD4 count of the case with hearing loss. Information related to social circumstances was only available for the case with normal hearing. She was cared for by a

single working parent who had completed grade 9. The family income was reported to the R66000 per annum.

***Reflections.*** A teacher who has these two cases in their class may expect the case with hearing loss to display more learning difficulties than the case with normal hearing, as compromised capacity to learn is less obvious than hearing loss. For the case with normal hearing, being classified as WHO Stage 3 (Iloh et al., 2017) and being schooled in a language that was not her primary language (Ouane & Glanz, 2011) may have negatively affected her neurocognitive skills. An additional factor that may be associated with compromised neurocognitive skills is the use of Efavirenz (Hammond et al., 2019), particularly long-term use (Ma et al., 2016).

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## Discussion

Case studies are currently making resurgence in scientific literature (Carey, 2010; Heale et al., 2016). They are being promoted as a way of interpreting group data into the real world, where healthcare providers, educators, or policymakers are required to make decisions on how best to manage individual cases (Plsek & Greenhaugh, 2001; Greenhalgh, Howick, Maskrey, 2014; McLean, 2016). Moreover, case studies enable patient complexities and individual issues to be explored in a way that cannot occur in large sample studies (Greenhalgh et al., 2015).

When designing experimental studies, inclusion criteria must be carefully considered to ensure homogeneity of groups, and hence, comparability. Greenhalgh, Thorne, and Malterud (2018) argue that the increasing elegance of group designs potentially loses sensitivity that is inherent in individual cases. Sufficiently large sample sizes have been seen to provide confidence to end users regarding the generalizability of findings (Faber & Fonseca, 2014). However, when individual cases are complex, as is evident from the research reported in this dissertation, combining data into groups for analysis is likely to mask important findings that can inform clinical, policy, and educational practices (Plsek & Greenhaugh, 2001). For this reason, case studies were felt to be informative in the current study.

One of the drivers for undertaking this research was to assist CLHIV to make the most of their educational opportunities. International research on preteens with HIV has raised awareness that CLHIV continue to be affected by their diagnosis despite the enormous positive benefits of ART. The complex sociodemographic issues surrounding CLHIV in South Africa highlights the likelihood that CLHIV who do not do as well as they could

educationally may also be dealing with issues such as living in poor, single-parent families (or being the responsible carer for ill parents or younger siblings), being unable to study because of overcrowding at home, or not having access to a well-balanced diet (Sekgoka, Mothiba & Malema, 2013). The reluctance of many parents to provide details on home circumstances in this study highlights the difficulty in identifying and interrogating the factors that could be related to compromised learning, but the low annual income of the families of children recruited provides some insight in this regard.

While this study focused on CLHIV, it was also clear that CNLHIV may experience barriers (social and medical issues) that could constrain their capacity to learn. These case studies also suggest that teachers may struggle to provide appropriate assistance to children who are not learning to their capacity, irrespective of their hearing deficits or HIV status. Decreased auditory functioning may present as inattention or behavioural problems, when, in fact, it may reflect undiagnosed hearing loss or a true neurocognitive barrier to learning.

It is also important to note that teachers in primary schools in the poorer socio-economic areas of metropolitan Cape Town often have fewer supports than teachers in wealthier schools (Pienaar & McKay, 2014). They may, for instance, have large classes and fewer teacher aides - if any. And parents may be unable to assist in the class, or even at home because they are working or have limited literacy.

A teacher's knowledge of the child's social and medical history is also an important variable to consider: These dyads suggest that children who are taking Efavirenz, or who have experienced TB/Malaria infection in the past or have a disconnect between their home and school language, may be at risk of poorer auditory functioning and the capacity to learn. A teacher who is not aware of these details, may not understand the impact thereof upon the

child's performance. Thus, relying only on the group statistics to provide evidence for learning difficulties experienced by CLHIV, and their peers who are HIV negative, is insufficient to highlight the extent of barriers to the next generation of South Africans in making a better life for themselves.

Despite best efforts, the small numbers in case and control samples in this study were unavoidable because of the previously unforeseen barriers to recruitment. Nonetheless, they served to highlight pertinent issues that can be further explored in future studies.

### **Key Learnings**

Teachers need to be alerted to the fact that there may be children in their class who are at unforeseen risk of not learning efficiently due to medical and social issues. In addition to information related to these medical and social issues, profiles of learners' auditory functioning and learning capacities would enable teachers to design teaching activities that are mindful of the learners compromised capacities. For example, avoiding presenting complicated multiple-step instructions to a learner who has reduced WM capacity (Cowan, 2014).

## Chapter 8

### Discussion

This chapter discusses the findings, as well as the limitations of the study. Although research related to hearing has included the preteen population, to the researcher's knowledge, no research has been reported on auditory processing capacities in this population. This population group has been neglected as HIV research has typically focussed on the developmental effects of HIV in young children or long-term consequences in adults.

Given the paucity of information on auditory functioning in the preteen population, this study sought to describe hearing loss, auditory processing capacities and learning capacities, in preteens living with HIV.

In particular, the study sought to address the following objectives:

1. Describe a profile of hearing in CLHIV and CNLHIV;
2. Describe a profile of auditory processing in CLHIV and CNLHIV;
3. Investigate the predictor variables associated with hearing loss in CLHIV;
4. Test the association between auditory functioning (hearing and auditory processing) and learning capacities (NVIQ, STM and WM) in CLHIV and CNLHIV

### Hearing profile of CLHIV and CNLHIV

#### *Prevalence of Hearing Loss*

The prevalence of hearing loss for the study population, consisting of both CLHIV and CNLHIV, was 19%. This was higher than expected as a previous study conducted in Cape Town reported estimated prevalence rates of hearing loss of 4.3% for children aged four to nine years and 2.6% for children aged 10 to 19 years (Ramma & Sebothoma, 2016). Three possible reasons for the higher prevalence rate are considered.

Firstly, the current study included a high percentage of CLHIV; a population reported to have a higher prevalence of hearing loss (Ianacone et al., 2017; Nakku et al., 2017; Matas et al., 2006, 2010; Palacios et al., 2008; Taipale et al., 2011; Chao et al., 2012; Makar et al., 2012; Torre et al., 2012; Torre et al., 2015; Hrapcak et al., 2016; Maro et al., 2016; Matsekete et al., 2014) which may have contributed to the higher prevalence rate observed in the study sample. Approximately one-third of the CLHIV presented with hearing loss. Although this finding is lower than that reported by Buriti et al. (2013), where included children were not all on ART, it is similar to other studies, also using pure tone audiometry, that reported on hearing loss prevalence rates ranging from 17% to 39% (Ianacone et al., 2017; Nakku et al., 2017; Matas et al., 2006, 2010; Palacios et al., 2008; Taipale et al., 2011; Chao et al., 2012; Makar et al., 2012; Torre et al., 2012; Torre et al., 2015; Hrapcak et al., 2016; Maro et al., 2016; Matsekete et al., 2014).

Furthermore, the cut-off criteria for hearing loss in this study differed depending on the site at which the children were tested, with 15dBHL being used for tests undertaken in a soundproof booth (Northern & Downs, 2002) and 25dBHL being used for tests undertaken in quiet environments. Ramma and Sebothoma (2016) only used 25dBHL as the cut-off criteria for normal hearing, and the lower cut-off point that was used in this study for CLHIV may have resulted in a higher prevalence of hearing loss than what was reported by Ramma and Sebothoma (2016).

Lastly, “volunteer bias” should be considered as a likely reason for the high prevalence rate. “Volunteer bias” is a systematic error that occurs because the participants who volunteer to participate in a study may be different to the general population (Salkind, 2010). The possibility exists that parents who consented to their children participating in the

study, were concerned about their child's hearing and agreed to the study as it provided an opportunity for the parent to address their concerns.

Comparing prevalence rates across studies is difficult as these rates are not only influenced by the testing methods used but are also dependent on the demographics of the population being tested.

### ***Type of Hearing Loss***

Due to the testing methods used for CNLHIV, the type of hearing loss was only determined for CLHIV. Despite all the CLHIV in this study being on HAART, CLHIV presented with conductive hearing loss more often than any other type of hearing loss. Conductive hearing loss, which is generally associated with middle ear infections, has been reported as the most common type of hearing loss in HIV positive children (Ensink & Kuper 2017). These findings are consistent with those reported by Palacios et al. (2008), Matas (2010), Chao et al. (2012), Matsekete et al. (2014), Torre et al. (2015), Hrapcak et al. (2016), Nakku et al. (2017) and Smith et al. (2017). The successful rollout of ART has resulted in reduced rates of opportunistic infections in CLHIV (Gona et al. 2006). Although HAART has been reported to decrease the occurrence of opportunistic diseases, time of treatment initiation appears to have an impact on the incidence of middle ear pathologies. Hainline et al. (2011) reported that early initiation of ART was associated with a greater decrease in the incidence of middle ear pathology than deferred initiation. Nakku et al. (2017) similarly reported an inverse relationship between duration of ART and hearing loss. These findings correlate with those of the current study as hearing loss was strongly associated with lifetime exposure to HAART. These findings suggest that deferred initiation or periods of noncompliance with HAART has an impact on hearing and by implication middle ear health

(conductive hearing loss). However, due to the small sample, Type I error should also be considered.

### **Profile of Auditory processing capacities in CLHIV and CNLHIV**

Auditory processing capacities were only assessed in participants with normal hearing. Performance on these tests was generally poor for both CLHIV and CNLHIV, with almost half (48.8%) presenting with poor auditory processing scores. All participants in this study came from lower socio-economic backgrounds and many were multilingual. Thus, both socio-economic status (Kraus & Anderson, 2015) and language (Loo, Bamiou & Rosen, 2013) should be considered as possible reasons for the participants' poor performance.

CLHIV performed significantly poorer than CNLHIV on the AFG and CWFR tests ( $p < 0.05$ ). These results correlate with the study hypothesis as auditory processing capacities were expected to be poorer in CLHIV. Romero et al. (2016) reported poor performance in CLHIV for dichotic speech and attributed the poor performance to attention and memory. When considering the well-documented neurocognitive effects of HIV (Crowell et al., 2014; Laughton et al. 2013), the effect of working memory and cognitive ability on auditory processing (Moore, 2011) needs to be considered: (a) auditory processing disorders are defined as “difficulties in the perceptual processing of auditory information in the central nervous system and the neurobiological activity that underlies that processing” (American Speech-Language-Hearing Association, 2005); (b) HIV causes disruption in CNS activity, with subsequent neurocognitive impairment. Thus, cognitive ability and its effect on auditory processing capacities (Tomlin et al., 2015) is an important consideration when assessing CLHIV.

Another important variable to consider in this study is the effect of home language on tests that are language-based. Although home language was not significantly associated with

the AFG or CWFR tests, a greater percentage of children who performed poorly, did not have English as their home language. However, based on the small sample size, the probability of a Type II error occurring should also be considered.

When examining the performance on the GD tests, although the difference was not significant, there was a trend towards significance ( $p=0.06$ ), with the majority (60.7%) of CNLHIV meeting the pass criteria compared to a third (33.3%) of CLHIV. Although Maro et al. (2016) reported similarly findings to this study, that CLHIV did not perform significantly poorer than CNLHIV, the lack of significance for both studies may have been due to the small sample.

The use of factor weighting, albeit on a small sample provides a better indication of the relative importance of the individual components than simply combining binary (1,0) forms of each measure into a composite score. Providing the data in two separate ways gives readers the opportunity to consider individual auditory processing measures or one composite measure. Individual scores may assist in planning therapy goals, but composite scores are useful as a screening tool to determine which children should be referred for diagnostic assessment.

### **CLHIV: Variables associated with hearing loss**

The only variable in this study that was significantly associated with hearing loss, was lifetime exposure to HAART. The findings therefore suggest that treatment should be initiated as early as possible to reduce the likelihood of hearing loss. These findings are consistent with Nakku et al. (2017), who reported a direct relationship between duration of ART use and hearing impairment.



### **HIV status, auditory functioning and learning capacities**

The study results supported the hypotheses, namely, that HIV status is related to poorer learning capacities in children with, and without, hearing loss; that HIV status is related to auditory processing capacities in children with no hearing deficits. Gender and primary language spoken at home, or school, did not appear to be related to auditory processing performance and learning capacities, and auditory processing appeared to be strongly and positively correlated with learning capacities in children without hearing deficits. The findings also suggested that STM might be affected for CLHIV with normal hearing, whose lifetime exposure to ARV was less than 75%. Furthermore, it can be said that there are complex causal pathways for paediatric auditory processing, HIV status, ARV lifetime exposure, and learning capacities, and that these require further investigation in larger samples (Hill, 1965).

Overall, an average performance for learning capacities was obtained for our sample (Brown, Sherbenov & Johnsen, 2010) (TONI 4 percentile rank score of 25 to 75). However, after stratifying the sample by HIV status, the CLHIV performed significantly poorer (with percentile rank scores corresponding to “below average” ratings) than the CNLHIV (rated “average”). These findings agree with those reported by Laughton et al. (2013) in their review of 11 studies on the neurocognitive effect of HIV. One of the impacts of HIV reported by these authors was poorer school performance and lower non-verbal scores than those of CNLHIV. HIV has been shown to negatively impact neurocognitive development with the major neurocognitive disorder being reported for simultaneous processing, planning, and nonverbal index on the Kaufmann Assessment Battery for Children – second edition (Musindo et al., 2018). Similar findings were also reported for 9-15-year-old children, with CLHIV performing at a “below average” rating on tests of verbal and reading ability

(Brackis-Cott et al. 2009). Although these tests differ from the nonverbal test used in our study, these verbal tests are also considered to measure cognition. These authors noted that the poor outcomes on the cognition tests were not necessarily related to HIV, as the children's performance was similar to that of children in studies of uninfected participants living in poor neighbourhoods. This notion that poverty influences cognition is supported by Sherr et al. (2009) as they suggested that neurocognitive ability was not necessarily a result of HIV status, but that family, environment, and treatment also influenced this ability.

### ***Causal Path***

The analysis undertaken in this research was based on a theory-driven, hypothesised causal path using the Bradford Hill (1965) mechanisms of causality (Appendix D). This causal path described HIV as an antecedent cause of auditory processing and hearing loss (exposures), with the primary outcome of nonverbal intelligence (learning capacity). However, the mechanisms by which HIV or its treatment impacts children's ability to process auditory information are not understood (Dawood et al., 2019), and this study demonstrated that even if CLHIV have normal hearing, they can have significant deficits in their auditory processing capacities. How auditory processing capacities relate to nonverbal intelligence is also unclear, as is the directionality of the relationships (de Wit et al., 2016; Tomlin et al., 2015).

HIV is now widely considered to be a chronic condition, and many CLHIV are living relatively normal lives, with near-normal life expectancy, on medications that manage their HIV infection (Melhuish & Lewthwaite, 2018; Gates & Cysique, 2016; Lewthwaite & Wilkins, 2009). However, like other chronic diseases, living with HIV may be associated with co-morbid conditions, such as dyslipidaemia (Innes et al., 2015; Tadesse et al., 2019). Socio-economic factors may further impact on the effects of living with the virus because it is

known that HIV is associated with lower socio-economic circumstances (Bunyasi & Coetzee, 2017; Steinert et al., 2017). Thus, CLHIV have been reported as having a greater burden than might be suspected because not only are they dealing with their health, but they often have family circumstances where parents/caregivers are also affected by HIV (Newlin, Reynold, & Nombutho, 2016; Pufall et al., 2014). This could mean ill or deceased heads of families, parent unemployment due to ill health, or poor living circumstances due to low family income (Pufall et al., 2014). Moreover, it may mean that families are headed by grandparents (Mtshali, 2016), extended family, or children themselves (Newlin et al., 2016).

### **Clinical implications of study**

**Improving their Circumstances.** South Africa is an economically and culturally diverse country with a large inequity in opportunity, income, employment, education, and health status (Sulla & Zikhali, 2018). CLHIV must therefore be empowered to improve their circumstances; otherwise, the same poverty cycle as affects many of their families will influence their chances in adulthood (Sulla & Zikhali, 2018). One way to assist children living with HIV is to ensure that they have educational opportunities at least as good as their uninfected peers (Spaull, 2013; Statistics South Africa, 2017). In most South African classrooms, learning occurs through the exchange of auditory information between educator and learner. This requires the learner not only to hear properly but also to process the information they hear in order to make sense of it. The mechanism by which HIV affects hearing in children is believed to be primarily through conductive mechanisms (Ensink & Kuper, 2017), which can be affected by opportunistic infections such as middle ear infections. This is the area in which HAART has had the greatest impact, in that it has reduced the child's susceptibility to opportunistic infections (B-Lajoie et al., 2016; Gona et al., 2006). A middle ear infection is the most common cause of hearing loss in all children,

irrespective of HIV status, with the incident peaking at two and five years (Robb & Williamson, 2016). Attending a day-care, limited breastfeeding, seasonal changes, passive smoking (Robb & Williamson, 2016), and low socio-economic status (Hunt et al., 2017; Karppinen et al., 2019). Hearing loss, however transient, can impact children's language, ability to learn, and social interaction (Madell, Hewitt, & Rotfleisch, 2018).

**The Emerging Impost of Living with HIV.** This research showed that while hearing loss prevalence is no longer greater in CLHIV compared to their uninfected peers, there are other constraints on these children's capacity to learn. For instance, a child's inability to localise sound and listen to speech in noise may result in compromised ability to listen effectively in confusing and noisy environments (e.g., a typical classroom) (Bamiou, Musiek, & Luxon, 2001). Furthermore, poor auditory discrimination has been linked to reading and spelling difficulties, while poor auditory pattern recognition has been linked to difficulties following oral instructions (Bamiou et al., 2001).

This study suggests that there may be a relationship between the inability to process auditory information and learning capacities. Thus, healthy CLHIV with normal hearing should still be considered as learners with special educational needs (Tikly & Barrett, 2011). Undiagnosed auditory processing difficulties, although invisible, has the potential to severely impede a child's capacity to learn (Tomlin et al., 2015), and by implication, their long-term capacity to leave the poverty trap. Thus, CLHIV have potentially less visible problems than they might have had previously, i.e., they are not sick (B-Lajoie et al., 2016; Gona et al., 2006); however, they may be carrying an equally problematic burden of the disease that is no longer as visible or easily addressed. By implication, health and educational services in South Africa therefore need to recognise the new wave of ramifications of HIV and plan for these by providing appropriate educational opportunities to CLHIV.

**Measuring Auditory Processing.** The systematic scoping review undertaken when first framing this research identified only five studies on auditory processing capacities in CLHIV. The evidence was inconclusive regarding the association between HIV, and auditory processing difficulties as the studies did not necessarily assess the same auditory processing capacities, and findings were, therefore, not comparable (Dawood et al., 2019). As a result, the limited data could not be used to guide the development of the auditory processing test battery that was constructed for this study. Auditory processing was, therefore, reduced to auditory processing capacities as these skills were measurable. Currently, there is no standard internationally accepted comprehensive auditory processing test battery (British Society of Audiology, 2018; Keith, 2009b). While this precludes best practice measurement of this construct, it may also be contributing to the hidden nature of auditory processing deficits. Moreover, current auditory processing test batteries include tests that require intact language systems and are, therefore not suitable for use across linguistically and culturally diverse populations (DeBonis, 2015). Future research in auditory processing should include functional assessments (e.g. questionnaires) that are less susceptible to the influences of cognition, language and socio-economic background of the child.

### **Critique of study**

**Overview of Sampling Concerns.** Children with and without HIV may come from varying SES backgrounds, for instance, single or no-parent families, low income homes, low caregiver literacy, poor understanding of hygiene, little understanding on how to optimize learning (Poudel et al., 2017; Pufall et al., 2014; Sekgoka et al., 2013). These complex and interrelated issues make robust sampling difficult, and assumptions need to be made regarding the homogeneity of sample estimates. One assumption is that children who live in the same suburb, irrespective of their HIV status, will have similar sociodemographic

characteristics. This is similar to studies using postal/zip codes. However, in South Africa, this assumption may not necessarily hold for all residents of a suburb and can lead to misclassification bias, as suggested by Lieu & Dewan (2010). The vestige of Apartheid, specifically the Group Areas Act of 1950, is that South African suburbs and towns are still segregated on racial lines, rather than purely on socio-economic lines, as people were forcibly moved to areas based on their classified race (Khalfani & Zuberi, 2001).

South Africa is a culturally and racially diverse country with 11 official languages (South African Government, n.d.-b), of which three are official in the Western Cape - namely English, Afrikaans and isiXhosa (Western Cape Government: Department of Cultural Affairs and Sport, 2019). Children are variably fluent in at least two of these languages because they are required to study two languages (home language and first additional language) in all South African schools (Department of Basic Education, n.d.). Depending on the language in which they are taught in school, there may be a mismatch between the language spoken at home and educational language, with resultant academic difficulties in the learning environment (Taylor & von Fintel, 2016). Thus, performance on assessment measures, which were typically only available in English, may have been compromised due to the mismatch between language of assessment and home language.

**Sampling CLHIV.** An unexpected difficulty was encountered when recruiting CLHIV for this study. Opportunities to access South African population registers are governed by strict legislation, Protection of Personal Information Act 4 of 2013 (South African Government: Department of Justice, 2013), thus access to the population registers of CLHIV were limited, which constrained robust sampling. This was known before study commencement, and thus, a purposive, personal recruitment approach was designed. In the Western Cape of South Africa, it was expected that most children with HIV would be taking

ART in line with provincial health policy (Provincial Government of the Western Cape: Department of Health, 2018). Thus, accessing children through an IDC in one large tertiary hospital in the Western Cape, which serviced a large socioeconomically disadvantaged population, was considered to be an appropriate recruitment site. What was not clear until recruitment started was the reticence of many parents/caregivers attending with the child on their follow up appointment, to enrolling their child in the study. However, Hudson et al. (2017), in their review of 215 studies looking at recruitment strategies in children with life-threatening conditions, reported similar issues. There were many reasons for recruitment difficulties including parent reluctance to take the child out of school for testing; concern with the child being involved with even more research (there were many concurrent research projects on CLHIV being conducted at this hospital); and perhaps less well articulated, concerns that the child's health status would become known at school and thus would attract stigmatisation. Moreover, participation in this research required parents/caregivers to complete a questionnaire that required a level of literacy, and despite offers to assist them to complete the questionnaire verbally, they were still reluctant. The possible reasons for poor recruitment in this study concur with those that have been reported for other studies involving children with other medical conditions (Hudson et al., 2017; Nguyen et al., 2014).

Incentives in the form of a free, comprehensive hearing test was offered. Control children received this at school, while CLHIV were required to travel to the tertiary hospital to receive it. Their parents were given a small travel allowance. Hearing screening is not routinely provided in South African primary schools despite its importance being recognised in the Integrated School Health Policy (Department of Health & Department of Basic Education, 2012). Thus, the children who participated in this study had the opportunity to access screening which would normally involve traveling to public health facilities offering

this service or paying for it in the private sector. Although the policies exist to support universal hearing screening within the school environment, implementation has been hampered by poor collaboration between the various stakeholders and lack of resources (trained staff and equipment) resulting in many children not being tested (Lenkokile et al., 2019; Rasesemola et al., 2019).

**Sampling CNLHIV.** There were similar, unexpected findings when recruiting control children (uninfected). However, poor recruitment has similarly been reported by Mirick (2016) for non-probability sampling. Initially, it was hoped that sufficient CNLHIV could be recruited to enable matching with CLHIV for age, gender, language, and educational grade. However, very similar barriers to recruitment were found for controls, and considering that non-probability sampling was used for both groups, similar issues can be expected (Mirick, 2016). Some schools are aware of children's HIV status, but there are ethical restrictions on disclosing this information. Thus, one school was chosen (Full-service school) as the source of controls because HIV status was known to the school administration. No personal, face-to-face contact was made with parents/caregivers to discuss the study (as was possible for parents/caregivers of CLHIV). Thus, recruitment of controls required parents reading, understanding, and replying to a written invitation sent home with the child. Although literacy may have been an issue in this sample, Mirick (2016) and Hudson et al. (2017) has also reported on the difficulties in executing research where there are multiple levels of gatekeeping (school, parent and child) as "buy-in" may occur at one level but enrolment into the study is not guaranteed. Given the several reasons why parents may not have responded and the concerns of three parents who refused participation, it appears that better sampling strategies are also required to recruit larger numbers of uninfected children.



**Potential Biases.** The small study sample was disappointing and constrained confidence in the findings. Similar low recruitment rates, where less than 50% of eligible participants were recruited, were reported by Hudson et al. (2017). While most of our findings reflected others' research findings, the wide variability in our findings highlighted the potential for Type II errors, as well as the need for further research. We suspect that volunteer bias influenced the sample as, anecdotally, some parents said that they wanted their child to be tested because they suspected a problem. These parents were, therefore, motivated to enrol their child into the study. According to Lieu & Dewan (2010), self-selection resulting in volunteer bias has been reported in studies about hearing loss and possible reasons for parents agreeing for their child to participate was that they would receive confirmation or additional information about an issue of concern. Another concern was that parents of CLHIV who had low levels of literacy and who did not speak the same language as the investigator, it may have been easier to refuse permission initially or to agree to participate and then fail to attend (as happened for 48.9% of consenting CLHIV). For parents of controls who had low levels of literacy and who received the written invitation via the school, it may have been easier to refuse permission or not return the form, than to find out more about the study. Thus, parents from both groups may not have had sufficient health knowledge to consider the benefits of participation (DeWalt & Hink, 2009). Moreover, due to ethics requirements, the invitation letter spoke about HIV and thus some parents of control children may have misinterpreted the intent of the study and the role that their child might play therein (Hudson et al., 2017).

**Measurement of learning capacities.** The relationship between capacity to learn, school performance, auditory processing difficulties, as well as hearing loss, has been established in children but largely in the global North (de Wit et al., 2016; Lesicko & Llano,

2017; Tomlin et al., 2015). Adding HIV status and its attendant socio-economic concerns in the diverse country that is South Africa complicates this causal relationship. There is no standard definition for learning capacity, nor is there an agreed test. Different assessments for the capacity to learn may include verbal IQ, non-verbal IQ, and academic progress (e.g., achievement in reading) (Lakin, 2012). Given SA's language diversity, race and family circumstances, the choice of a non-verbal measure of capacity to learn was likely to provide the least biased measure and to ensure that no child was discriminated against (Brown et al., 2010; DeThorne & Schaefer, 2004).

Not all children were able to complete the working memory tests because intact hearing was a requirement as a hearing loss would impact performance (Martin & Brownell, 2005).

**Language Disconnects.** Our findings suggest that children who learn in a language other than their home language may be disadvantaged in terms of an opportunity to learn (Taylor & von Fintel, 2016; Prinsloo, Rogers, & Harvey, 2018). These children may be misdiagnosed as having cognitive difficulties when in fact, they are simply struggling with the mismatch between home and school, particularly if the home environment does not support them to achieve their best (Taylor & von Fintel, 2016). Examples of this may be where caregivers do not speak the academic language, are illiterate, are drug or alcohol affected, chronically unwell, too young or old to assist the child, or absent from home for long periods because of migrant work. Moreover, one of the post-apartheid legacies is the continuing reality that despite the integration of three schooling systems (white, coloured, black) into one, there remains inequity in terms of school resources (McKeever, 2017). Some parents choose to send their child to a school where the home language is not spoken on the perception that their child will receive a better education. This may disadvantage the child

who has to learn in a different language and culture, which becomes exponentially more difficult if the child has auditory processing problems (Prinsloo et al., 2018).

**Reflections on the Data.** There was a large amount of missing data from hospital records, which precluded extraction of information on important measures such as CD4 count, viral load, compliance with ART, and other medical histories that may have impacted the child's auditory processing capacities and learning capacities. Moreover, parents were universally reluctant to provide medical, social, and academic information on their family, and it was impossible to find information from independent school records on child scholastic performance because access was denied. Incomplete information was provided by some teachers and this was not sufficient to enable interrogation of scholastic performance, capacity to learn, and auditory processing. Difficulties in accessing accurate records reflected the difficulties of obtaining information in low socio-economic environments where lack of money, time, and standard databases compounded the availability of standard, easily accessed information as might expected in a first world country.

The clinical nature of the data used in this study provided both advantages and disadvantages.

The advantages were that it reflected clinical data collected under clinical conditions.

Therefore, any relationships found between the screening and diagnostic test results for APD would reflect relationships that exist under clinical rather than laboratory conditions. The disadvantages were that it contained missing data that required the use of case-wise (and, in one instance, list-wise) deletion of missing data in the correlation and regression analyses and because it was likely to contain errors of a clinical nature that might have been avoided under laboratory conditions.

There were several key learnings from this research:

1. Barriers to robust recruitment in preteen CLHIV and uninfected children from low socio-economic areas in South Africa should be better understood before future study commencement. This will enable environment-specific recruitment strategies to be developed that address the concerns of parents/caregivers in giving consent for their children to participate in research;
2. There is a need for a comprehensive and ubiquitous test battery for auditory processing that is appropriate for any child, in any circumstance;
3. The TONI 4 was an appropriate measure of (nonverbal intelligence) learning capacity because it was accessible to all children , irrespective of hearing loss or primary home language;
4. Hearing loss was a concern for both preteen CLHIV and uninfected children;
5. CLHIV without hearing loss had poorer auditory processing capacities than their CLHIV, and their auditory processing scores correlated with their NVIQ;
6. Children who did not learn at school in their home language (mostly children with an African home-language) appeared to perform more poorly on the auditory processing tests and the learning capacity tests, compared with children who learned in their spoken home language;
7. The educational needs of pre-teen children with hearing loss, or HIV, should be considered on an individual basis;
8. A preliminary audit of the medical records of CLHIV should have been undertaken to identify data items that were likely to be incomplete, so that this could be sourced elsewhere during data collection. Moreover, permission should have been sought from children's parents and their schools in order to access information on school performance, including absenteeism;

9. Future research into auditory processing and learning capacity of preteen South

Africans should aim to:

- a. Collect larger samples so that case complexities can be better understood by robust subgroup analysis. This will require a more robust sampling frame based on qualitative research findings, which have identified the reasons underpinning parents' or caregivers' reluctance to allow their children to participate in research.
- b. Develop a comprehensive list of data items that explores not only the objective measures of auditory functioning and learning capacity but also social factors that may impact negatively on a child's educational performance.
- c. Use multiple measures that reflect clinical, as well as research imperatives, and which enables all children to participate equitably in testing, irrespective of HIV status, hearing loss, or primary home language. Measures are required to determine hearing loss relevant to the testing environment, provide access to all potentially-useful measures for auditory processing for children with intact hearing, and use a measure of non-verbal intelligence (learning capacity) that does not discriminate against children with hearing loss, or whose primary home and school languages differ.
- d. Explore the impact on auditory processing and cognition, of ART and drugs for TB/Malaria, in preteen children who need the best start possible to their learning.

10. Teachers need to be alerted because there may be children in their class who may be at unforeseen risk of not learning efficiently because of medical and social issues.

While HIV status may be known, there may well be other factors, of which teachers

and parents may be unaware, that compromises the child's educational potential.

While the findings reported in this dissertation are not sufficiently robust to spark immediate action (because of the potential for Types I and II error), they do flag the notion that a risk profile could be developed of children who may struggle to achieve their academic potential. Such a risk profile could alert teachers to alternative explanations as to why a child is not doing well in class. Moreover, a risk profile could be applied at the beginning of any new school year, to assist the teacher to understand which children may benefit from closer monitoring.

## Chapter 9

### Conclusion

This study attempted to use non-discriminatory methods to assess auditory functioning and nonverbal intelligence in preteen children with different language and cultural backgrounds, from a low socio-economic environment in metropolitan Cape Town, South Africa. An equitable way of measuring auditory processing was proposed, despite the lack of an industry standard. Sampling and recruitment issues compromised the power of this study in producing believable findings, as well as generalisability of findings. These issues were unexpected, as was a large amount of missing data in hospital records and from parents. Despite this, this study adds to the scarce body of knowledge about the auditory processing capacities of children who live with chronic HIV and its impact on their capacity to learn. This appears to be significantly poorer than in uninfected children. Ensuring that preteen children have the best possible opportunities in life begins with maximizing their learning potential. Preventing hearing loss in children with and without HIV, from low socio-economic backgrounds, is only one element thereof. The more subtle implications of living with HIV on children's capacity to process auditory information, and learn, would appear to be the next challenge for healthcare professionals and educators.

Further studies are urgently needed in this area to ensure that CLHIV are not disadvantaged in achieving their learning potential. Studies should first concentrate on optimising recruitment by understanding why parents in low socio-economic environments, are reluctant to provide consent for participation in studies such as these. From what was learned in this study, this was a problem irrespective of the child's HIV status. Developing recruitment strategies that are contextually relevant, and address barriers to recruitment in

low socio-economic areas in South Africa are therefore essential to ensure that future studies have sufficient power.



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## Appendices

### Appendix A

#### Submitted Paper: HIV and hearing loss

##### **Hearing loss in a group of HAART-treated 9-12 year old children from Cape Town, South Africa: A cross-sectional study**

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Title: Hearing loss in a group of HAART-treated 9-12 year old children  
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Keywords: HIV, hearing loss, auditory impairment, antiretroviral therapy,  
Highly active antiretroviral therapy

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Grimmer

Abstract: Introduction: In South Africa, HIV affects approximately 1:3  
children under 12 years. Most children commence antiretroviral therapy  
(ART) as soon as they are diagnosed. Amongst other health benefits, ART  
protects children from opportunistic infections; such as chronic ear  
conditions, which can result in hearing loss. However, living with HIV  
as a chronic disease may challenge children's health and development in  
other ways.

Objectives: In this study we investigate the prevalence of hearing loss  
in a group of 9 to 12 year old, school going children, test for  
associations between hearing loss and key physiological, health history  
and family circumstance predictor variables.

Methods: Children (HIV positive) were consecutively recruited from the  
Infectious Disease clinic at a XXX tertiary hospital servicing a low  
socio-demographic area. Audiologic assessments comprised parent  
questionnaire, otoscopy, tympanometry and pure tone testing from 250  
through 8000 Hz. Hearing loss was defined as a pure tone average (500Hz,  
1000Hz and 2000Hz) greater than 15db hearing level (HL) assessed in a  
soundproof booth. Descriptive statistics and measures of association were  
reported.

Results: Data was collected on 23 eligible, consenting children, aged 9  
to 12 years old. Hearing loss prevalence was 34.8%. There was a  
significant association between hearing loss and less than lifetime  
exposure to ART, OR = 4.4 (95% CI 1.1-18.5). There was no association  
between hearing loss and any other variables.

Conclusions: The findings suggest that hearing loss, perhaps related to  
opportunistic infections such as middle ear infection, continue to be  
present in HIV infected children, despite them being on highly active  
antiretroviral therapy (HAART). This may be associated with non-exposure  
to ART at some stage during their lifetime, which may have been due to  
late diagnosis, late initiation of HAART or non-compliant periods.

Research Data Related to this Submission

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## INTRODUCTION

South Africa continues to have the biggest HIV epidemic globally <sup>1</sup> and is currently home to 260 000 [200 000–360 000] children living with HIV, aged 0–14 years, with new infections in this age group reported to be 14 000 [11 000–35 000] per year <sup>2</sup>.

However, South Africa also has the most extensive antiretroviral (ARV) programme in the world <sup>1</sup>. This has resulted in near-normal life expectancy for the approximately 163 000 children, or 63% [49–87%] of infected children, who are on ARVs <sup>1,2</sup>. For these children, HIV is no longer considered a terminal disease but rather a chronic condition that may be accompanied by various disabilities <sup>3</sup>, including hearing loss <sup>4</sup>.

High prevalence of hearing loss has been reported in both HIV-infected adults and children, with the bulk of the literature on adults <sup>4</sup>. Estimated prevalence in the paediatric population varies from 6% to 84% depending on the assessment measure used, as well as the age of the children <sup>4</sup>.

Many variables have been associated with hearing loss, including the HIV disease itself, ARV use, opportunistic infections such as otitis media, meningitis and tuberculosis, as well as ototoxic treatment for opportunistic diseases <sup>4</sup>.

The aim of this study was to investigate the prevalence of hearing loss in a group of 9 to 12 year old, school going children, and to test for associations between hearing loss and key physiological, health history and family circumstance predictor variables.

## METHODS

*Ethics:* This research was approved by the Health Research Ethics Committee of XXX University on 22 March 2016 (Reference number S15/10/220). Permission for conducting the study was also obtained from the XXX Department of Health (XXX DoH) and the relevant

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4 tertiary hospital where recruitment occurred. Written informed consent was obtained from  
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6 children, and their parents/caregivers after the study had been explained to them.  
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10 *Sample reported for this paper:* This study reports on cases (HIVP children) recruited for a  
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12 larger study (which was an unmatched case-control study of HIVP and HIVN children aged 9-12  
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14 years).  
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17 *Source of HIVP children:* One large tertiary metropolitan hospital in XXX provided access to  
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19 paediatric HIV cases attending its Infectious Diseases Clinic (IDC). This hospital provided  
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21 services for over 3.4 million people in surrounding socioeconomically disadvantaged suburbs,  
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23 most of whom relied on public health care.  
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27 *Sampling:* Convenience sampling occurred at point of contact with the IDC between June 2017  
28  
29 and November 2018, although consecutive sampling occurred on each recruitment day. This  
30  
31 was the most efficient approach to recruit HIVP children to this study<sup>5</sup>, to deal with the difficulty  
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33 in accessing comprehensive records for random subject selection, parent suspicion of being  
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35 approached by researchers, stigma, or the problem of HIVP children being over-researched).  
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40 *Sample size calculation:* The IDC at the participating tertiary hospital had records of 836 patients  
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42 on ART at the end of February 2017. This included 412 children (aged 0 to 18 years). Attempts  
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44 were made to recruit all 110 children who were aged 9-12 years, and who were on the register to  
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46 attend the IDC for medical follow up appointments. The IDC operates from Monday to  
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48 Wednesday (8h00 – 13h00), with the majority of paediatric appointments available on Tuesdays.  
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50 The researcher attended the IDC and physically identified and recruited eligible children on each  
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52 clinic day. Each morning, the medical records (folders) of all children with appointments for the  
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54 particular day were accessed at the IDC, and the researcher identified all potential candidates  
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56 based on their date of birth. Children's caregiver(s) attending the appointment with them were  
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approached and informed about the study. If they were interested, the child's eligibility was confirmed by questioning, and if caregivers consented, the child was enrolled in the study. A small reimbursement for travelling costs was offered to each family to assist in bringing the child for testing.

*Inclusion and exclusion criteria:* Boys and girls were included if they had: (1) documented HIVP status; (2) were aged between 9 – 12 years; (3) had verbal proficiency in at least one of English, XXX or XXX language; (4) were enrolled in at least Grade 3 in a mainstream primary school; and (5) had the ability to understand and complete a consent form. Exclusion criteria were: (1) comorbid conditions causing cognitive impairment (e.g. neurological conditions) that could affect understanding of, and performance in, the assessment batteries; (2) cognitive impairment (e.g. intellectual disability) that could affect understanding of and performance on the assessment test batteries; or (3) on a waiting list for, or enrolled, in a school for learners with special education needs.

*Study measures:* We tested for hearing loss, and collected caregiver reports and/or case note information on lifetime exposure to ARVs, history of serious illness likely to affect hearing (malaria, TB or meningitis); gestational age, birthweight, current CDC4 count, estimate of viral load, World Health Organisation HIV stage, school performance, caregiver relationship to child, caregiver marital status, employment capacity and level of education; and family income.

*Hypotheses:* We tested:

1. The prevalence of hearing loss (HL);
2. Whether HL was associated with predictor variables including:
  - a. Lifetime exposure to ARVs;
  - b. CDC4 count and viral load;

- c. Gestational age
- d. history of repeating school grades, or absence from school;
- e. history of meningitis, TB or malaria; and
- f. family circumstances (person in caregiver role, level of caregiver education, family income).

*Measurements:* A standard case history was taken by interview from the primary caregiver as the initial step in the paediatric audiologic test battery<sup>6</sup>. This provided important information regarding the nature of the auditory complaint, possible contributing factors, developmental progress, communication abilities and academic achievement<sup>6</sup>. Information was corroborated or expanded by reviewing the child's case history. The case history interview also included relevant health and medical information, as well as information on the child's academic progress and hearing capabilities. If the caregiver preferred, the questions were administered verbally in their chosen language (i.e. English, XXX or XXX). The interview format allowed the primary investigator to probe for answers where necessary, and to clarify questions that were not understood<sup>5</sup>. This was only done when the caregiver was unable to provide an adequate response. In addition, the verbal administration of the questionnaire ensured that caregivers were not excluded based on literacy levels. In all instances however, to ensure consistency of data collection, question wording was strictly adhered to, as it appeared on the questionnaire.

An otoscopic examination investigated the condition of the outer ear and tympanic membrane using a Welch Allyn pocket otoscope<sup>6</sup>. This was included in the test battery to determine abnormalities of the outer ear and tympanic membrane, reported in people who are HIV positive<sup>7</sup>. Abnormalities such as inflammation, growths, foreign objects, excessive wax or

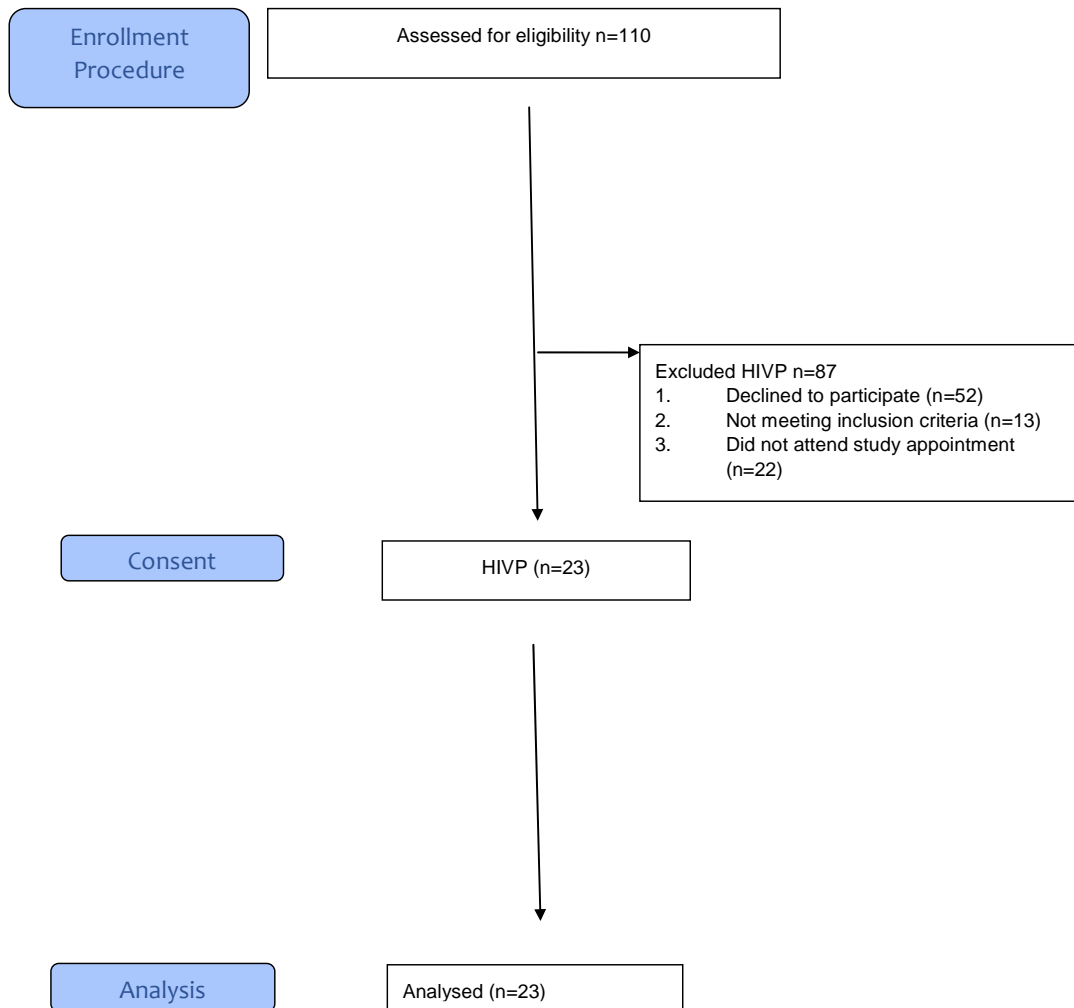
perforations of the tympanic membrane were recorded on the audiogram. If abnormality was noted, the child was referred to the treating doctor for medical management.

Tympanometry was conducted to assess the transmission of sound through the middle ear<sup>6</sup>. This component of the test battery was included, as research has reported an increase in abnormal middle ear function in persons with HIV<sup>7</sup>. After the audiologist explained the procedure, tympanograms were obtained using a GSI Tymptest with a 226 Hz probe tone. The pressure direction was from positive to negative (200 to -400daPa). The results were recorded on the audiogram, and the following parameters were used to indicate normal middle-ear function: Type A tympanogram with a middle ear pressure of -100 to =100 daPa; acoustic compliance of 0.3 to 1.7 ml; and ear canal volume of 0.4 – 1.5 ml. Participants presenting with abnormal tympanograms were referred to the treating doctor (IDC) or their closest clinic for medical management. Pure tone audiometry was conducted to determine the behavioural hearing thresholds of each participant as well as the type of hearing loss<sup>6</sup>. This component of the test battery was included as research reports that hearing loss is associated with HIV<sup>8,9</sup>.

Pure tone audiometry was performed in a sound proof booth, using a GSI 61 audiometer. Circum-aural earphones were used and air conduction thresholds were obtained at 250Hz, 500 Hz, 1000 Hz, 2000Hz, 4000Hz, 8000 Hz as per conventional audiometry<sup>6</sup>, for the left and right ears separately. All thresholds were plotted on an audiogram. Bone conduction threshold testing was only conducted at frequencies where the air conduction threshold was >15dBHL, to determine the type of hearing loss; i.e. conductive, sensorineural or mixed hearing loss. If bone conduction threshold testing could not be completed, tympanometry results were used to differentiate between conductive and sensorineural hearing loss. Any participant presenting with

## RESULTS

Figure 1 outlines the recruitment procedure and numbers recruited, of HIVP children (cases)



**Figure 1.** CONSORT Diagram for case children

**ART descriptors:** Data was available for all 23 cases regarding ART history. Considering the percentage of the child's life spent on ART, the average percentage of life spent on ART was 78.5% (SD 20.7%) (range 23-6% - 100%). All children were on HAART, with 22 of the children (95.6%) being on 3TC; N=21 (91.3%) being on ABC; N=16 on Aluvia (69.5%); N=7 (30.4%) on EFV; N=1 on TDF and N=1 on AZT. Six children (28.6%) had a history of defaulting on ART.

**Hearing loss:** Eight children (14 ears) had hearing loss in one or both ears (34.8% total cases). Six of these children had bilateral hearing loss, with the remaining two children presenting with unilateral hearing loss. The unilateral cases were only in the right ear. Of the 14 ears presenting with hearing loss, nine ears (64.2%) presented with conductive hearing loss (associated with middle ear pathology) and five ears presented with sensorineural hearing loss.

The mean PTA-Right was 15.2 (12.7) and PTA-Left was 12.6 (9.9). The mean overall severity score of hearing loss in the left ear was 0.4 (SD 0.8), and in the right ear it was 0.6 (SD 0.9). For hearing loss in both ears the severity score was 1.0 (SD 1.7).

**Factors associated with hearing loss:** CD4 count was only available from the casenotes of 11 children, precluding analysis of associations with HL. Only ART lifetime exposure less than the median (80.6%) provided evidence of an important association with hearing loss.

**Table 1.** Associations between HL in either ear and predictor variables

Variable	Cut point	Odds ratio (95%CI)
ART lifetime exposure	<80.6%	4.4 (1.1-18.5)
History of defaulting on ARV	Yes	1.0 (0.2-7.4)
WHO staging	Stages 3 or 4	1.9 (0.5-7.9)
Viral load	LDL	1.7 (0.3-9.1)
Disease history	TB, malaria, meningitis	2.6 (0.7-11.5)
Prematurity	<38 weeks gestation	0.6 (0.2-3.7)
Developmental delay	Any	1.7 (0.1-36.7)
History of absence from school	Yes	0.4 (0.1-3.4)
History of repeating grade	Yes	0.7 (0.2-3.6)
Age-for-grade	Grade 3 $\geq$ 10 years or Grade 4 $\geq$ 11 years or Grade 5 $\geq$ 12 years or 6 $\geq$ 13 years	2.6 (0.6-10.9)
Family income	< R28320 / year	1.7 (0.3-8.8)
Parent care giver	No	1.6 (0.3-9.2)
Care giver education	Completed Grade 10 or lower	0.4 (0.1-1.6)



## DISCUSSION

This study provides further information for the scant current body of evidence regarding the prevalence of hearing loss in 9 to 12-year-old South African children, who are currently on HAART. Given their recruitment from a low socioeconomic environment (supported by evidence of parent education and family income in this study), these children were potentially exposed to opportunistic infections associated with poor nutrition, cramped living quarters and poor hygiene. Findings suggest that hearing loss in this sample was primarily conductive in nature, despite the common use of HAART. This was supported by the finding that hearing loss was associated with a less than 80% lifetime exposure to ART.

Approximately one third of the sample presented with hearing loss. Although this finding is lower than that reported by Buriti et al<sup>14</sup>, where included children were not all on ART, it is similar to other studies, also using pure tone audiometry, that reported on hearing loss prevalence rates ranging from 17% to 39%.<sup>7, 8,15-22, 23-25</sup>

The strong finding of conductive hearing loss in our study suggests that this could be associated with middle ear pathologies, despite all the children being on HAART. These findings are consistent with those reported in the literature.<sup>8-9,16-17,19,22-23,25</sup> Although HAART has been reported to decrease the occurrence of opportunistic diseases, including middle ear pathologies, early initiation of ART has been found to decrease the incidence of otorrhea to a greater extent than deferred initiation of ART<sup>26</sup>. As hearing loss in our study was strongly associated with lifetime exposure to ART, it suggests that the longer it takes to commence ART, or period of

noncompliance with ART has an impact on hearing. These findings are consistent with Nakku et al<sup>8</sup> that reported a direct relationship between duration of ART use and hearing loss.

## CONCLUSION

Our findings suggest that hearing loss continues to be present in HIV infected children, despite them being on HAART. It may be related to opportunistic infections such as middle ear infection associated with non-exposure to ART at some time during their lifetime (due to late diagnosis, late initiation of HAART or non-compliant periods).

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## Appendix B

Submitted Paper: HIV, hearing loss and learning capacity

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**1 HIV, hearing loss and learning capacity in Cape Metropole pre-teens, South Africa: A cross-**

**2 sectional study**

**3**

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## ABSTRACT

**Background:** In South Africa, HIV affects approximately 1:3 children under 12 years. Most children commence antiretroviral therapy (ART) as soon as they are diagnosed. Amongst other health benefits, ART protects children from opportunistic infections; such as chronic ear conditions, which can result in hearing loss. However, living with HIV as a chronic disease may challenge children's health and development in other ways. This paper tests associations in children aged 9-12 years, HIV status, hearing loss and learning capacity.

**Methods:** Case children (HIV positive) were recruited from the Infectious Disease clinic at a South African tertiary hospital servicing a low sociodemographic area. Control children (HIV negative) were recruited from a school in a surrounding suburb. Audiologic assessments comprised parent questionnaire, otoscopy, tympanometry and pure tone testing from 250 through 8000 Hz. Hearing loss was defined as a pure tone average (500Hz, 1000Hz and 2000HZ) greater than 15db hearing level (HL) assessed in a soundproof booth (cases), or greater than 25dBHL assessed in a quiet school environment (controls). The Test of Nonverbal Intelligence (TONI 4) percentile rank scores were used to assess learning capacity. Descriptive statistics and measures of association were reported.

**Results:** Data was collected on 56 children (42.8% cases, 57.2% controls). There was no association between hearing loss and HIV status (OR 2.8 [95%CI 0.8-10.1]). TONI 4 scores differed significantly between cases and controls (control mean scores 39.5% (SD 18.5%), case mean scores 21.4% (SD 10.1%)). There was a significant association between HIV status, and binary division TONI 4 scores (OR 15.4 (95%CI 3.7-63.8)). There was no association between hearing loss and learning capacity (loss in one ear OR 0.8 (95%CL 0.1-6.2), loss in both ears OR 1.3 (95%CI 0.1-15.7)).

**Conclusions:** Lack of association between hearing loss and HIV status suggests that ART may be protecting case children from opportunistic infections that result in hearing loss. The strong association between HIV status and learning capacity suggests that other factors may be impacting on neural

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46 development. This has implications for educational policies, as HIV positive children potentially require

47 additional support to fully participate in available learning opportunities.

48 *Keywords:* HIV, hearing loss, auditory impairment, learning, nonverbal intelligence



## 49 BACKGROUND

50 People are living for longer with HIV as with better medical management it is now a chronic disease,  
51 rather than a terminal one (Nixon et al. 2011<sup>a</sup>). Seven million people are currently living with HIV in  
52 South Africa, with 320 000 (260 000 – 400 000) of these being children between the ages of 0 and 14  
53 years (World Health Organization 2017). Although the prevalence of HIV in children has declined since  
54 2002, with better mother-child transmission prevention practices (Shisana et al. 2014), new infections  
55 continue to occur, with the World Health Organization (2017) estimating that 12 000 (9600 – 22000)  
56 South African children became infected in 2016.

57 Despite these new infections, the initiation and maintenance of ART programmes has had a positive  
58 impact on the fight against HIV (Mayosi et al. 2012). Advances in ART, in particularly the introduction  
59 of Highly active antiretroviral therapy (HAART), has been associated with decreased mortality (Patel et  
60 al. 2008) and a reduction in opportunistic diseases (Gona et al. 2006) in the paediatric population.

61 Globally, 55% (45% - 70%) of infected children aged between 0 and 14 years, are receiving ART (World  
62 Health Organization 2017) and are thus expected to live longer lives. The status of HIV has thus changed  
63 from a life-threatening disease to a chronic disease, with accompanying consequences that may challenge  
64 the rehabilitation, health and social sectors in resource-poor settings (Gates & Cysique 2016; Nixon et al.  
65 2011<sup>b</sup>; Nixon et al. 2011<sup>a</sup>; Worthington et al. 2009).

66 Hearing loss is considered to be associated with HIV (Ensink & Kuper 2017; Torre 2015). Adult-based  
67 studies suggest a higher prevalence of hearing disorders (such as hearing loss, tinnitus and vertigo) in  
68 HIV positive individuals (compared to HIV negative individuals), as well as changes that the disease  
69 itself may produce in the auditory system (Khoza-Shangase 2010; Maro et al. 2014; van der Westhuizen  
70 et al. 2013). Possible reasons for the hearing disorders include the HIV infection itself, opportunistic  
71 infections resulting from reduced immunity, or ototoxicity from factors such as ART, or repeated  
72 treatments for opportunistic infections (Khoza-Shangase 2010).

73 Abnormal audiological findings related to HIV status have also been reported in paediatric studies (Buriti  
74 et al. 2013; Christopher et al. 2013; Devendra et al. 2013; Hrapcak et al. 2016; Nakku et al. 2017; Smith  
75 et al. 2017; Torre et al. 2015). Although all these studies report on abnormal findings, the studies that  
76 have included control groups have differed with regards to whether the prevalence of hearing loss in HIV-  
77 positive and HIV-negative children are significantly different. Torre et al. (2015) and Nakku et al. (2017)  
78 did not find significant differences in hearing loss prevalence rates between these children while Smith et  
79 al. (2017) found HIV-infected children had a significantly higher occurrence of hearing loss than HIV-  
80 negative children.

81 Children with hearing loss have reduced access to auditory information, which among other constraints,  
82 can result in reduced exposure to spoken language and subsequent delays in listening and language  
83 development, as well as in difficulties with academic work (Madell et al. 2018; Northern & Downs 2002).  
84 The degree of hearing loss does not necessarily affect the magnitude of academic difficulties as poorer  
85 learning outcomes (namely, language and literacy and the child's approach to learning) have been  
86 reported by teachers for children with slight to mild hearing loss when compared to children with normal  
87 hearing (Wang et al. 2019).

88 The effect of hearing loss on learning is not only due to a lack of access to auditory information but also  
89 due to fatigue associated with hearing loss (Gustafson et al. 2018; Key et al. 2017). Children with hearing  
90 loss show reduced attention and fatigue during difficult listening tasks and may, therefore show a reduced  
91 ability to focus on classroom instruction (Gustafson et al. 2018). They may, therefore, process auditory  
92 information that has been presented, inefficiently as learning within a class environment requires  
93 sustained attention (Key et al. 2017).

94 HIV has not only been associated with hearing loss but also with other neurocognitive deficits that can  
95 affect learning (Govender et al. 2011). Developmental delays, including delays in cognitive development,  
96 have been described in HIV-infected children (Kerr et al. 2014) with major neurocognitive disorder and  
97 difficulties at school being reported (Musindo et al. 2018). HIV-related effects on learning may not only

98 be as a direct consequence of having the disease, but may also be due to the indirect consequences of  
99 living with the virus, or living with an adult who has the virus (Guo et al. 2012). HIV positive children  
100 may be more prone to illness, and have poorer school attendance due to sick days, or medical  
101 appointments (Anabwani et al. 2013).

102 In South Africa, poorer learning outcomes and poorer performance on cognitive tests have also been  
103 reported for children from low socioeconomic environments (Maswikiti 2008). According to Hackman et  
104 al. (2010) there are three classes of mechanism to explain the effects of socioeconomic status on the brain  
105 and cognition; *first*, prenatal influences that can affect early brain development (e.g. impaired fetal growth  
106 and poor nutrition during pregnancy), *second*, parental care factors that could influence  
107 neurodevelopment, such parent-child interaction and parental sensitivity towards the child, and *third*, the  
108 level of cognitive stimulation in the home environment such as the availability of books and educational  
109 outings.

110 Measuring cognitive skills is challenging, particularly when considering that the constructs that are  
111 measured are not relevant across all cultures and languages (Holding et al. 2018). For the purposes of this  
112 study, nonverbal intelligence was used as a proxy for learning capacity as this would eliminate the effect  
113 of socioeconomic variables and linguistic, cultural and literacy differences (Brown et al. 2010). Although  
114 nonverbal intelligence is less robust in predicting academic outcomes than verbal intelligence, it reflects  
115 fluid intelligence abilities (Dethorne & Schaefer 2004). Fluid intelligence is defined as “the innate  
116 learning capacity of an individual, not dependent on education or experience, which is used with  
117 relatively novel tasks, reasoning, and information analysis. Based on the Cattell-Horn theory of  
118 crystallized and fluid intelligence” (APA PsycNET n.d.) and describes the ability to use inductive and  
119 deductive reasoning to identify patterns and relations, and to make inferences (Dethorne & Schaefer  
120 2004). These mental operations occur independent of prior knowledge and predicts performance on a  
121 range of cognitive skills (Horn & Cattell 1966). The use of a nonverbal measure was therefore considered  
122 a more valid method of measuring learning capacity.

## METHODS

*Aim:* This study was undertaken to assess whether chronic HIV status in children on long-term ART, was still associated with hearing loss, and whether learning capacity was affected. This paper explores the associations between HIV status, hearing loss and learning performance in children aged 9-12 years in a low socioeconomic South African metropolitan area.

*Study context:* One large tertiary metropolitan hospital in Cape Town provided access to paediatric HIV cases attending its Infectious Diseases Clinic (IDC). This hospital provided services for over 3.4 million people in surrounding socioeconomically-disadvantaged suburbs, most of whom relied on public health care. In South Africa, only 17% of citizens is estimated to have medical insurance, resulting in the majority attending public health facilities (South African Government n.d.). A tertiary hospital is a public hospital to which more complex cases are referred, however in this instance, the participating hospital also provided an ART clinic to patients who were unwilling to be transferred to local community level health facilities.

*Sample:* This study investigated school learners aged 9-12 years who had confirmed HIV positive status (HIVP) or reported HIV negative status (HIVN)). The sample was not age-or gender-matched.

*Sampling:* Convenience sampling at point of contact with the healthcare system, or school, was used to recruit children in both HIVP and HIVN groups. Convenience sampling was considered to be the most efficient approach to recruit children to this study (Babbie 2010), to deal with the complexities of recruitment in low socioeconomic circumstances (difficulty in contacting potential subjects when not attending health appointments or school, parent literacy, difficulty in accessing comprehensive records for random selection of subjects, parent suspicion of being approached by researchers, stigma, constraints on attendance at appointments, being over-researched etc).

*Inclusion and exclusion criteria:* Males and females were included if they had: (1) documented HIV-positive status or reported HIV-negative status; (2) were aged between 9 – 12 years; (3) had verbal

147 proficiency in at least one of English, Afrikaans or Xhosa language; (4) were enrolled in at least Grade 3  
148 in a mainstream primary school and (5) had the ability to understand and complete a consent form.  
149 Exclusion criteria were: (1) HIV status not documented/reported; (2) comorbid conditions causing  
150 cognitive impairment (e.g. neurological conditions) that could affect understanding of, and performance  
151 in, the assessment batteries; (3) cognitive impairment (e.g. intellectual disability) that could affect  
152 understanding of and performance on the assessment test batteries; or (4) on a waiting list for, or enrolled,  
153 in a school for learners with special education needs.

154 *Recruiting the HIVP group:* The IDC at the participating tertiary hospital, had records of 836 patients on  
155 ART at the end of February 2017. This included 412 children (aged 0 to 18 years). Attempts were made  
156 to recruit 110 children attending the IDC for their medical follow up appointments, between June 2017  
157 and November 2018. The recruitment process involved the researcher attending the IDC and physically  
158 identifying and recruiting children on each clinic day. The IDC operates from Monday to Wednesday  
159 (8h00 – 13h00), with the majority of paediatric appointments available on Tuesdays. Each morning, the  
160 medical records (folders) of all children with appointments for the particular day were accessed at the  
161 IDC, and the researcher identified all potential candidates based on their date of birth. Children's parents  
162 were approached and informed about the study. If they were interested, the child's eligibility was  
163 confirmed by questioning the parents, and if parents consented, the child was enrolled in the study. A  
164 small reimbursement for travelling costs was offered to each family to assist them to bring their child for  
165 testing.

166 *Recruiting the HIVN groups:* Children were recruited from one local primary school in the same area as  
167 the participating hospital. Information pamphlets were distributed to 137 children aged 9-12 years in this  
168 school, together with informed consent forms and the researcher's contact telephone number. The school  
169 was considered as a full-service school by the WCDoE, where the children's HIV status was known by  
170 the school. The school principal assisted the researcher in distributing research information only to  
171 children who were noted as not being infected with HIV.

**172** *Causal relationships:* Because of the lack of clarity in the literature to unravel the complexity of putative  
**173** associations between HIV status, hearing loss and learning capacity, the Bradford Hill criteria for causality  
**174** (Hill 1965) was applied to map a likely causal path that underpinned analysis. The role of HIV was difficult  
**175** to place in this model as it was a plausible antecedent cause for hearing loss (with the disease and/or its  
**176** treatment affecting structures of the ear), but it also could plausibly have a direct relationship with learning  
**177** capacity (as time spent away from school for illness or medical treatment, which could interrupt learning).  
**178** Being on ART for HIV could also have had a biochemical influence on learning capacity.

**179** For this study, we proposed that HIV status acted as an exposure variable in a causal pathway in which  
**180** hearing loss was an interim outcome, and where learning capacity was the final outcome (Rothman 1985).  
**181** As all children came from the same sociodemographic areas, we assumed that their socio-economic status  
**182** was also similar. Potential confounders on the association between HIV and hearing loss, and hearing loss  
**183** and learning capacity were proposed as gender because girls have been reported to perform better  
**184** academically than boys (Kingdon et al. 2017; O'Dea et al. 2018) and language as the language of schooling  
**185** is a reflection of educational inequalities that continue to be a legacy of Apartheid (McKeever 2017).

**186** *Hypotheses:* We tested four associations relevant to the causal path.

- 187** 1. HIV status, hearing loss and learning capacity are all associated with gender;
- 188** 2. There are significant associations, all confounded by gender, and language of schooling between:
  - 189** a. HIV status and hearing loss,
  - 190** b. HIV status and learning capacity; and
  - 191** c. Hearing loss and learning capacity.

**192** *Measurement procedures:* Step 1. A case history was taken from the primary caregiver. This is the initial  
**193** step in a paediatric audiologic test battery (Stach 2010). This typically provides important information  
**194** regarding the nature of the auditory complaint, possible contributing factors, developmental progress,  
**195** communication abilities and academic achievement (Stach 2010). For this study, the case history  
**196** interview was conducted to gain the relevant health and medical information, as well as information on

197 the child's academic progress and hearing capabilities. This information was also used to identify possible  
198 clinical complexities (such as history of opportunistic disease).

199 A standard questionnaire was used to elicit the case history, although it was delivered differently for HINP  
200 and HIVN participants. For the HIVP group, if the caregiver preferred, the complete set of questions were  
201 administered verbally in their chosen language (i.e. English, Afrikaans or isiXhosa). The interview format  
202 allowed the primary investigator to probe for answers where necessary, and to clarify questions that were  
203 not understood (Babbie 2010). This was only done where the caregiver was unable to provide an adequate  
204 response. In addition, the verbal administration of the questionnaire ensured that caregivers were not  
205 excluded based on literacy levels. In all instances however, to ensure consistency of data collection,  
206 question wording was strictly adhered to, as it appeared on the questionnaire. For the HIVN group, the  
207 case history questionnaires were sent home with the child, as the caregivers were not present during testing.  
208 Caregivers were requested to complete the questionnaire and return it to school, in a sealed envelope, where  
209 the primary investigator collected it. Literacy levels were not taken into account for this group as it was  
210 assumed that the parents/caregivers could consult with literate neighbours or family members if they  
211 required assistance.

212 Step 2. An otoscopic examination was conducted in order to investigate the condition of the outer ear and  
213 tympanic membrane (Stach 2010). This part of the assessment was included in the test battery as there are  
214 reports about abnormalities of the outer ear and tympanic membrane in patients who are HIV positive  
215 (Ianacone et al. 2017). After the procedure was explained to the participant, an audiologist used a Welch  
216 Allyn pocket otoscope to examine the relevant structures. Abnormalities such as inflammation, growths,  
217 foreign objects, excessive wax or perforations of the tympanic membrane were recorded on the audiogram.  
218 If abnormality was noted, the child was referred to the treating doctor for medical management.

219 Step 3. Tympanometry was conducted to assess the transmission of sound through the middle ear (Stach,  
220 2010). This component of the test battery was included, as research has reported an increase in abnormal

221 middle ear function in persons with HIV (Ianacone et al. 2017). After the audiologist explained the  
222 procedure, tympanograms were obtained using a GSI Tymptstar (HIVP group) and Interacoustics MT10  
223 (HIVN groups) with a 226 Hz probe tone. The pressure direction was from positive to negative (200 to -  
224 400daPa). The results were recorded on the audiogram, and the following parameters were used to indicate  
225 normal middle-ear function: Type A tympanogram with a middle ear pressure of -100 to =100 daPa;  
226 acoustic compliance of 0.3 to 1.7 ml; and ear canal volume of 0.4 – 1.5 ml. Participants presenting with  
227 abnormal tympanograms were referred back to the treating doctor (IDC) or their closest clinic for medical  
228 management.

229 Pure tone audiometry was conducted to determine the behavioural hearing thresholds of each participant  
230 as well as the type of hearing loss (Stach 2010). This component of the test battery was included as  
231 research reports that hearing loss is associated with HIV (Nakku et al. 2017; Smith et al. 2017).  
232 The same testing circumstances were not available for all children.

233 *HIVP group:* After the audiologist explained the procedure, pure tone audiometry was performed in a sound  
234 proof booth, using a GSI 61 audiometer. Circum-aural earphones were used and air conduction thresholds  
235 were obtained at 250Hz, 500 Hz, 1000 Hz, 2000Hz, 4000Hz, 8000 Hz as per conventional audiometry  
236 (Stach 2010), for the left and right ears separately. All thresholds were plotted on an audiogram.  
237 Participants were considered to have hearing loss if a pure tone average (PTA) of >15dbHL was obtained  
238 (Northern & Downs 2002). Bone conduction threshold testing was only conducted at frequencies where the  
239 air conduction threshold was >15dBHL. The bone conduction thresholds were obtained in order to describe  
240 the type of hearing loss; i.e. conductive, sensorineural or mixed hearing loss. Any participant presenting  
241 with a sensorineural hearing loss was referred to the Audiology Department at Tygerberg Hospital for  
242 diagnostic testing and further management. Any participant presenting with a conductive or mixed hearing  
243 loss was referred back to the treating doctor, at the IDC for medical management.



244 *HIVN group*: After the audiologist explained the procedure, the Pure Tone Audiometry was performed in a  
245 quiet venue, as provided by the school. Sound proof booths were not available at the school. Testing was  
246 completed using an Interacoustics AS608 screening audiometer. Circum-aural earphones were used and air  
247 conduction thresholds were obtained at 250Hz, 500 Hz, 1000 Hz, 2000Hz, 4000Hz, 8000 Hz as per  
248 conventional audiometry (Stach 2010), for the left and right ears separately. All thresholds were plotted on  
249 an audiogram. A participant was considered to have a hearing loss if a pure tone average (PTA) of >25dBHL  
250 was obtained (Northern & Downs 2002). Bone conduction was not conducted due to the limitations of the  
251 audiometer and testing room environment (Schlauch & Nelson 2009).

252 Due to the differences in testing conditions for the HIVP and HIVN groups, a pure tone average of less  
253 than or equal to 15dBHL (Northern & Downs 2002) for the HIVP group, and less than or equal to  
254 25dBHL for the HIVN group, was considered to constitute normal hearing. The pure tone average was  
255 calculated as the average of thresholds for 500Hz, 1000Hz and 2000Hz. The degree of hearing loss was  
256 classified as: minimal (PTA = 16 to 25dBHL), mild (PTA = 25 to 40dBHL), moderate (PTA = 41 to  
257 55dBHL), moderately-severe (PTA = 56 to 70 dBHL), severe (71 to 90 dBHL) or profound (greater than  
258 90dBHL) (Clark 1981 in (Welling & Ukstins 2015). Classification of type of hearing loss was based on  
259 the size of the air-bone gap (ABG). A hearing loss was considered to be conductive if the ABG was  
260 greater than 10dB, sensorineural if the ABG was less than or equal to 10dB (Stach 2010) and unspecified  
261 if bone conduction testing was not conducted.

262 Step 4. The Test of Nonverbal Intelligence – Fourth edition (TONI 4) was used as a proxy for learning  
263 capacity, as the test purports to measure aptitude, abstract reasoning and problem solving ability (Brown et  
264 al. 2010). The TONI 4 model is based on the premise that cognitive ability can be estimated by measuring  
265 the ability to problem solve. As the TONI 4 is not loaded with language and does not require the respondent  
266 to read, write, speak or even listen; the test is considered suitable to assess people with communication  
267 disorders (including hearing loss), learning disorders and those who are not proficient in English. The test  
268 items are arranged according to difficulty level (i.e. from easier to more difficult items) and, according to

the developers, performance is not influenced by familiarity with the items. The abstract nature of the items, as well, as the lack of language reduces the possibility of educational, cultural and experiential biases (Brown et al. 2010). However, the instructions were given in the preferred language of the child, with the parent present. The parent/caregiver was provided with a written translation of the instructions and was requested to give these instructions to the child. Where literacy was a problem, the researcher explained the instructions to the parent with the aid of the written translation and the parent then transmitted the information to the child. The percentile rank score was used and provided an indication of the percentage of the normative population that obtained a score equal to or below the score obtained by the participant (Brown et al. 2010)

*Data management:* Hearing loss was reported for the purpose of this study as none (0) or as three different types (conductive hearing loss (CHL), sensorineural hearing loss (SNHL) or unspecified) (all coded as 1) in left or right ear. “Unspecified” referred to hearing loss where the type of hearing loss could not be determined as bone conduction thresholds were not available.

The degree of hearing loss in each ear was recorded as mild (PTA = 25 to 40dBHL), moderate (PTA = 41 to 55dBHL) or severe (71 to 90dBHL) (Clark 1981 in (Welling & Ukstins 2015). The category “unspecified” was used when the hearing testing had not been conducted in a sound proof booth.

A cumulative integer score was determined for hearing loss as the per-child sum of severity scores (hearing loss (yes, no) in either ear multiplied by the numeric code given to the severity of loss. Hearing loss was then applied to models as a three-level variable (no hearing loss, hearing loss in only one ear, or hearing loss in both ears). A total severity score was calculated per child and reported as an integer variable for analysis of variance models. The higher the severity score the more severe the hearing loss. For logistic regression modelling purposes, the severity score was split into three independent variables (0 for children without hearing loss), and then at the median value of severity for children with hearing loss (>0 to 2 (mild hearing loss), >2 (moderate or severe loss)). For the purposes of analysis, the TONI 4 score was expressed as a percent of the possible total score, and this was also split at the median value for modelling purposes.

294 *Data analysis:* All data was described as frequencies or mean values (standard deviations), as appropriate.

295 Differences in potential confounders (gender, languages spoken at home and school), and outcome variables

296 (hearing loss, severity of hearing loss, and learning capacity) were estimated for two HIV groups (HIVP,

297 HIVN), and the significance of differences was calculated using  $\chi^2$  or ANOVA models, as appropriate.

298 Potential confounders which appeared to be important were retained for subsequent modelling.

299 To gain the most leverage from the sensitivity of the integer variables, linear regression models were

300 initially constructed to test the association between severity of hearing loss and learning performance

301 scores, using the Pearson  $r^2$  statistic as an estimate of strength of association (Katz 2006). The significant

302 predictor variables identified in initial testing were individually applied to this model with differences in

303 impact being determined as significant change in the  $r^2$  statistic.

304 Univariate logistic regression models were then constructed to test the association between binary forms of

305 HIV status with hearing loss (model 1), HIV status and learning performance (model 2) and hearing loss

306 and learning performance (model 3). Potential confounders were added to these models in a step-wise

307 manner applying the strongest predictor variable first. Predictor variables were retained in the model if

308 they significantly changed the amount of variance, determined from the chi square value associated with

309 the Likelihood Ratio, assessed against the critical chi square value for the degree of freedom associated

310 with the model (<https://web.ma.utexas.edu/users/davis/375/popecol/tables/chisq.html>).

311 At  $p < 0.05$ , for one degree of freedom, the critical  $\chi^2$  value is 3.8, for two degrees of freedom, it is 5.9 and

312 for three degrees of freedom, it is 7.8.

## 313 RESULTS

314 *Sample:* There were 110 cases identified at the IDC, who were potentially-relevant for recruitment. Of

315 these, 52 declined to participate, 12 did not meet the inclusion criteria and 22 did not attend their

316 appointment for testing (even after reminders were sent and/or appointments were rescheduled). This left

317 24 cases. Considering the controls, of the 137 information pamphlets and consent forms distributed at the

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3  
4 318 participating school, 34 consent forms were returned. Of these, two parents declined their child's  
5  
6 319 participation. This left 32 eligible controls with consenting parents. Thus, the dataset consisted of 56  
7  
8 320 children, of 24 cases (42.8%) and 32 controls (57.2%). Figure 1 outlines the study inclusion and exclusion  
9  
10  
11 321 flow diagram.

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14 322 <<Figure 1 here>>

15  
16  
17 323 *Demographics:* Thirty children were male (53.6%) and there were no gender differences between cases and  
18  
19 324 controls ( $p>0.05$ ).

20  
21 325       ○ Average age of children in the sample was 11.2 years (SD 0.9) (reflecting the age limits of 9-  
22  
23 326       12 years).

24  
25 327       ○ Children who were identified, in hospital or school records or by their parents on the case  
26  
27 328       history forms, as Coloured predominated (79.8%), with smaller percentages of children  
28  
29 329       identified as Black (19.1%) or White (1.1%);

30  
31 330       ○ English as a primary language, was spoken both at home and school by 31.7% sample,  
32  
33 331       Afrikaans as a primary language, was spoken both at home and school by 31.7% sample, and  
34  
35 332       other African languages (e.g. IsiXhosa) were spoken as primary languages both at home or  
36  
37 333       school, by 7.9% children;

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39 334       ○ Most children spoke the same language at home and school (87.5%).  
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42  
43  
44 335 *Hearing loss:* Eleven children overall (19.6% sample) were diagnosed with hearing loss (Yes/No), with  
45  
46 336       seven recording it in both ears (63.6% of those with hearing loss). Considering the entire sample (children  
47  
48 337       with, and without hearing loss), the overall severity of hearing loss score for either ear ranged from 0-3  
49  
50 338       (mean 0.3, SD 0.7), and the overall both-ear score ranged from 0-6 (mean 0.6, SD 1.4). Considering only  
51  
52 339       those children with hearing loss (all with severity ranges from 1-3), for children with Right ear loss only,  
53  
54 340       the severity score was 2.1 (SD 0.9), and for children with Left ear loss only, the severity score was 1.6 (SD  
55  
56  
57 341       1.1). The overall severity score for the seven children with hearing loss in both ears was 3.7 (SD 1.8).  
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342 *Learning capacity:* The mean TONI 4 percentile rank score was 31.8 (SD 17.8) ranging from 6-84.

343 *Demographics as a predictor of HIV:* Gender was not associated with HIV status (OR 0.7, 95%CI 0.2-1.9).

344 *Demographics as a predictor of learning capacity:* There was no influence of gender on learning capacity

345 (TONI 4 percentile rank scores (girls mean 33.0 (SD 18.1) and boys (36.1 (SD 21.2 (F value 0.4 (df=1)

346  $p>0.05$ ). There was a significant effect of speaking English at home on language performance scores (mean

347 TONI 4 percentile rank score 47.7 (SD 21.0), compared with Afrikaans language (mean 28.8 SD 14.1) and

348 African languages (mean 27.5, SD 18.3) (F value 8.3 (df=2)  $p<0.01$ )). There were similar significant

349 findings for languages spoken at school, with English school-language TONI 4 percentile rank scores being

350 significantly higher than the other school languages (English mean TONI 4 score 42.8 (SD 21.0), Afrikaans

351 mean 28.6 (SD 13.9) and African languages mean 14.8 (SD 8.7) (F value 8.1 (df=2)  $p<0.01$ )). Moreover,

352 there was no influence of experiencing a difference in languages spoken at home and school on TONI 4

353 percentile rank scores (same language mean 34.7% (SD 20.3%), different language mean 33.5% (SD

354 17.9%) (F value 0.04 (df=1)  $p>0.05$ ).

355 *HIV as a predictor of hearing loss and learning capacity:* Seven cases (29.1%) and four controls (12.5%)

356 were diagnosed with hearing loss, and there was no significant association between HIV status and hearing

357 loss (OR 2.8, 95%CI 0.8-10.1). This finding persisted when further considering the severity of hearing

358 loss. Compared with children with no hearing loss (severity=0), the association between HIV status and

359 minimal/ mild severity of hearing loss was OR 8.2 (95%CI 0.9-79.4) and for moderate/ high severity of

360 hearing loss, the association with HIV status was OR 2.1 (95%CI 0.4-11.3). Learning capacity was

361 significantly different between HIV status groups, with the controls having significantly higher TONI 4

362 scores (mean 39.5%, SD 18.5%) compared with mean TONI 4 scores for the cases (21.4% (SD 10.1%)).

363 Using the median division in TONI 4 scores (30%), there were significant odds that HIV status was

364 associated with low TONI 4 scores (OR 15.4 (95%CI 3.7-63.8)).

365 *Hearing loss and learning capacity:* The association between hearing loss and learning capacity was

366 considered in two ways, with neither demonstrating a significant association. Using both hearing loss and

learning capacity as integer variables in a linear regression model, there was a minimal association ( $r^2=1.0\%$ ,  $p>0.05$ ). Using categories of hearing loss of none (default comparator), one ear or both ears, and testing against learning capacity divided at the median value, there was no significant association for one ear (either Left or Right) OR 0.8 (95%CL 0.1-6.2), or both ears affected OR 1.3 (95%CI 0.1-15.7)). There were insufficient numbers of children with mild-moderate hearing loss to resolve a logistic regression model which considered three independent levels of hearing loss severity (none (default), mild-moderate or severe). Thus, a binary form of hearing loss severity data was developed, as none, or combined categories of mild, moderate and severe. There was no association between learning capacity and hearing loss categories (OR 3.5 (95%CI 0.9-13.5)).

*Multivariate analysis:* The only significant potential confounder for application to the multivariate model of HIV status (exposure) and learning capacity (outcome) was hearing loss severity. The crude and adjusted model outputs are reported in Table 1. The overall variance of the crude model (-2 Log L) was 87.3. The amount of variance explained by adjusting this model by hearing loss severity was not significant (less than the threshold significant chi-square value of 5.99 (df=2)).

**Table 1.** Findings from multivariate analyses of the association between HIV and learning capacity

Primary exposure	Potential confounder	OR (95%CI)	Likelihood Ratio	df	Chi <sup>2</sup> change	Critical chi <sup>2</sup> value for df	Sig of change
HIV+		(crude) 15.4 (3.7-63.8)	19.9	1		3.8	p<0.05

	Hearing loss severity	(adjusted) 21.1 (4.1-109.5)	20.4	2	0.5	5.9	p>0.05
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385

386 **DISCUSSION**

387 This study presents rare evidence about associations between HIV status, hearing loss and language-free  
 388 learning capacity in pre-pubescent South African children, sampled from one low socioeconomic  
 389 environment. The findings suggest that HIV was more strongly associated with learning capacity than it  
 390 was with hearing loss.

391 The causal pathway between these variables is potentially complex (Hill 1965), and how HIV influences  
 392 hearing loss and learning capacity in pre-teens requires further research. The causal model was constructed  
 393 on an assumption that hearing loss was the most proximal exposure for learning capacity. The role of HIV,  
 394 considered initially to be an antecedent cause of hearing loss, appears to operate in differently than we  
 395 anticipated. An increasing number of recent studies have reported on a significant relationship between  
 396 positive HIV status and hearing loss in children, and although our findings suggested no significant  
 397 difference, the prevalence of hearing loss in our cases (29.1%) and controls (12.8%) is similar to previous  
 398 reports (Chao et al. 2012; Hrapcak et al. 2016; Matas et al. 2010; Palacios et al. 2008; Smith et al. 2017;  
 399 Torre et al. 2015).

400 Our findings may well provide a view of current circumstances with HIV children, as ART had been  
 401 initiated early for case children, and all were currently on HAART. Therefore they were potentially less  
 402 susceptible to opportunistic infections than they previously would have been (Gona et al. 2006). Conductive  
 403 hearing loss, which is generally associated with middle ear infections, has been reported as the most  
 404 common type of hearing loss in HIV positive children (Ensink & Kuper 2017). The successful rollout of  
 405 ART, has resulted in reduced rates of opportunistic infections in HIVP children (Gona et al. 2006). Thus,

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4 406 HIVP children may now have the same susceptibility to infections as HIVN children, resulting in similar  
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6 407 rates of hearing loss.  
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9 408 The children all lived in the same low socioeconomic area (surrounding the case catchment hospital), and  
10  
11 409 thus our sampling approach assumed that all children had similar exposure to poverty. In the 25 years of  
12  
13 410 post-Apartheid South Africa, poverty continues to be related to race and the language spoken, with 64%  
14  
15 411 black South Africans and 46% Coloured South Africans believed to be living in poverty (Statistics South  
16  
17 412 Africa 2017). While our subjects were all potentially living in the same socioeconomic circumstances, our  
18  
19 413 sample was heterogenous in terms of race and language spoken (reflecting expected local area statistics).  
20  
21 414 This suggests that exposure to poverty rather than race and language spoken, may be the mediating factor  
22  
23 415 for hearing loss, or learning capacity for our cases and controls. The complex nature of the causal pathways  
24  
25 416 for paediatric hearing loss, HIV status and learning capacity requires further investigation (Hill 1965).  
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29  
30 417 *Association between HIV and hearing loss:* The prevalence of hearing loss for the study population (19%)  
31  
32 418 was higher than the estimated prevalence of hearing loss (3.2%) reported recently by Ramma & Sebothoma  
33  
34 419 (2016) on 4-19 year old children in Cape Town. One reason for this is that the Ramma and Sebothoma  
35  
36 420 (2016) study used 25dBHL as the cut-off point for normal hearing, whereas our study used 15dBHL for  
37  
38 421 tests undertaken in the sound proof booth, as recommended for children aged 0 to 18 years (Northern &  
39  
40 422 Downs 2002). This lower cut-off point that we used for the HIV-infected children may have resulted in a  
41  
42 423 higher prevalence of hearing loss than what was reported by (Ramma & Sebothoma 2016).  
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45  
46 424 *Association between HIV and learning capacity:* Overall, an average (TONI 4 percentile rank score of 25  
47  
48 425 to 75) performance for learning capacity was obtained for our sample (Brown et al. 2010). However, after  
49  
50 426 stratifying the sample by HIV status, the cases performed significantly poorer (with percentile rank scores  
51  
52 427 corresponding to “below average” ratings) than the controls (rated “average”). These findings agree with  
53  
54 428 those reported by Laughton et al. (2013) in their review of 11 studies on the neurocognitive effect of HIV.  
55  
56 429 One of the impacts of HIV reported by these authors, was poorer school performance and lower non-verbal  
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58 430 scores than HIVN children. HIV has been shown to negatively impact neurocognitive development with  
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major neurocognitive disorder being reported for simultaneous processing, planning and nonverbal index on the Kaufmann Assessment Battery for Children – second edition (Musindo et al. 2018). Similar findings were also reported for 9-15 year old children, with HIVP children performing at a “below average” rating on tests of verbal and reading ability (Brackis-Cott et al. 2009). Although these tests differ from the nonverbal test used in our study, these verbal tests are also considered to measure cognition. These authors noted that the poor outcomes on the cognition tests were not necessarily related to HIV, as the children performed in a similar manner to studies involving uninfected children living in poor neighborhoods. This idea that poverty may influence cognition is supported by Sherr et al. (2009) as they suggested that neurocognitive ability were not necessarily a result of HIV status, but that family, environment and treatment also influenced this ability.

*Limitations:* The cross-sectional design of the study does not allow for causal associations to be made. The non-significant differences in hearing loss prevalence may reflect Type II error from our small sample size. Moreover, as the sample was recruited from one tertiary hospital and surrounding suburbs within the Cape Metropole, the findings cannot be generalized more broadly. Likely systematic biases which would have been introduced in the pragmatic, circumstantially-driven strategies which we had to employ to recruit children. Although the control children were recruited from the same sociodemographic area serviced by the tertiary hospital, key variables such as race, home circumstances, noise exposure and history of previous ear infections between cases and controls could not be matched. Whilst this limits interpretation of the study findings, future studies seeking larger and more randomly-sampled subjects would have to employ innovative recruitment approaches to deal with the difficulties of recruiting children in low socioeconomic areas, for research in this sensitive health area.

## CONCLUSIONS

HIV status is significantly associated with learning capacity in children aged 9 to 12 years, but not hearing loss. The study findings suggest that the TONI 4 is an appropriate for children with hearing loss, as having a hearing disorder was not associated with poorer non-verbal scores. The association between HIV and

learning capacity has important implications for educational policies as HIVP children will probably need additional support to fully participate in the learning opportunities provided within the schooling system. The implication of these findings is that the learning needs of these children cannot be addressed by a uniform approach, and research into factors impeding full participation in learning opportunities should be investigated in order to provide evidence-based, appropriate learning support.

#### DECLARATIONS

*Ethics:* This research was approved by Stellenbosch University Human Research Ethics Committee (S15/10/220). Permission for conducting the study was also obtained from both the Western Cape Department of Health (WCDoH) and Western Cape Department of Education (WCDoE), as well as from the relevant tertiary hospital and primary schools. Written informed consent was obtained from children, and their parents/caregivers after the study had been explained to them.

*Consent for publication:* The informed consent forms included consent for publication.

*Availability of data and materials:* The dataset has been submitted with the manuscript

*Competing interests:* The authors do not have any competing interests

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*Authors' contributions:* Conceptualization and project design – GD, MP, DK; Data analysis and writing the paper – GD, KG; Editing of manuscript – GD, KG, MP, DK

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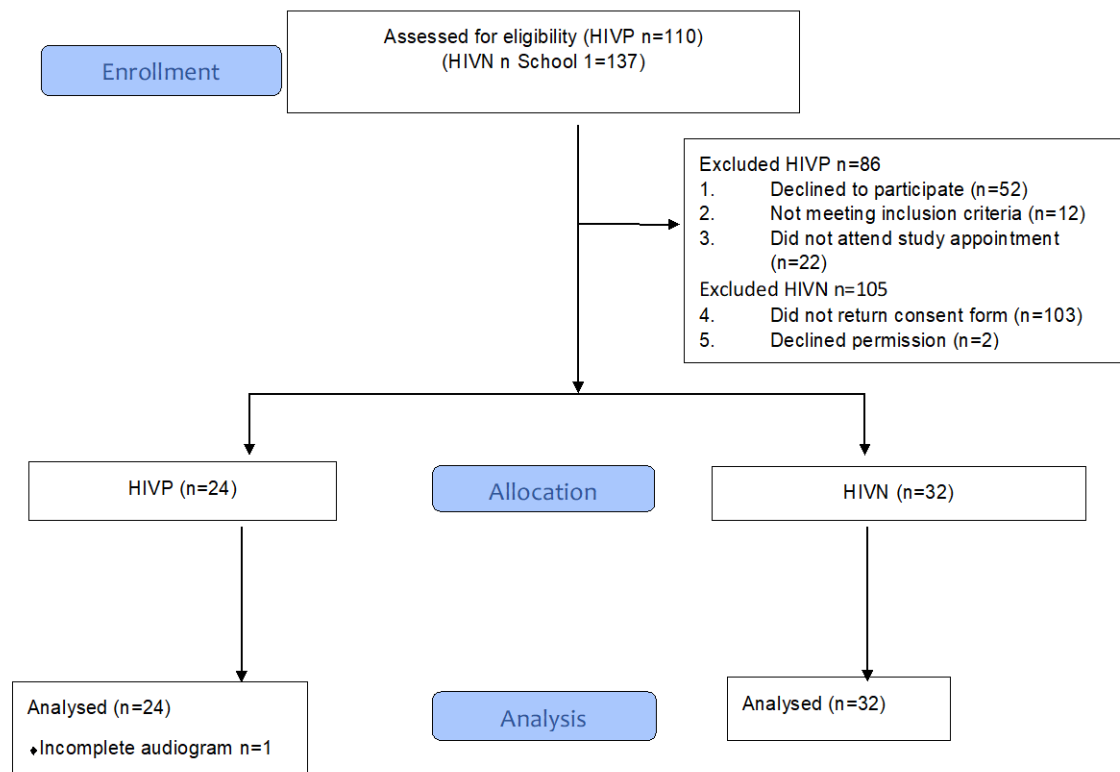
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Figure

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## Submitted Paper: Auditory processing, HIV status and learning capacity

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24

25 **ABSTRACT**

26 **Introduction:** The human immunodeficiency virus (HIV) affects 1.7 million children  
27 globally, with 260 000 of these children living in South Africa. Due to the impact of highly  
28 active antiretroviral treatment (HAART), HIV has evolved into a chronic disorder with  
29 children living with HIV (CLHIV) having near normal life expectancy. However, as with  
30 chronic disorders in children, other health and educational issues may arise. This paper  
31 tests associations between HIV status, auditory processing skills and learning capacity,  
32 in preteen children.

33 **Methods:** HIV-infected children (cases) were recruited from an Infectious Disease Clinic  
34 at a South African tertiary hospital, situated in a low sociodemographic area. HIV-  
35 uninfected children (controls) were recruited from a primary school in the surrounding  
36 suburb. Only children who were assessed (pure tone audiometry) as having normal  
37 hearing were included in this study. The Test of Nonverbal Intelligence Fourth Edition  
38 (TONI 4) was used to assess learning capacity. Auditory processing skills were assessed  
39 using subtests of the SCAN 3 for Children: Tests for Auditory Processing Disorder (Gap  
40 Detection, Auditory Figure Ground 8+ and Competing Words-Free Recall) and the Test  
41 of Auditory Processing Third Edition (TAPS), as well as sound laterality. Descriptive  
42 statistics and measures of association were reported.

43 **Results:** Data were reported on 43 children (15 cases, 28 controls) with normal hearing.  
44 CLHIV had significantly poorer learning capacity (mean cases 1.6 (SD 0.5) mean controls  
45 (0.9 (SD 0.7) ( $p < 0.05$ )) and had a greater risk for having poor auditory processing scores  
46 (OR 4.95 (95%CI 1.24-19.69) compared with uninfected peers.

47 **Conclusion:** A sampling frame sought to minimise differences for cases and controls  
48 for sociodemographic factors thus, it is unlikely that these factors were responsible for  
49 the differences in learning capacity and auditory processing. There must, therefore, be  
50 subtle factors related to living with HIV as a chronic disease, that explain the findings. If  
51 CLHIV are performing poorly in class, they should be referred for investigations of  
52 neurocognitive skills so that they can be provided with the support they need.

53

## 54 INTRODUCTION

55 Globally, an estimated 1.7 million children (aged 0 to 14 years) are living with the human  
56 immunodeficiency virus (HIV), with an additional 160 000 children being infected annually  
57 [1]. The widespread rollout of effective antiretroviral therapy (ART), coupled with  
58 adherence to the medication, has resulted in the life expectancy of these children being  
59 near normal [2]. Thus, HIV is now considered to be a chronic condition, with associated  
60 conditions that may require additional health, social and educational services [3].

61

62 Auditory impairments, including hearing loss [4] and difficulties with auditory processing  
63 [5], have been reported in children living with HIV (CLHIV). Auditory processing refers to  
64 “what we do with what we hear” [6] and comprises various processes or skills which are  
65 required to make sense of our auditory world. According to the American Speech-  
66 Language-Hearing Association (ASHA) these skills include: “sound localization and  
67 lateralization, auditory discrimination, auditory pattern recognition, temporal aspects of  
68 audition, auditory performance decrements with competing acoustic signals, and auditory  
69 performance decrements with degraded acoustic signals” [7]. Not only do these children

70 present with auditory processing difficulties, but poor speech, language, literacy, attention  
71 and academic performance have also been reported [8].

72

73 Auditory processing disorders have been associated with neurological involvement,  
74 including degenerative diseases and exposure to neurotoxic substances [9]. According  
75 to the American Psychological Association, “impairment in perceptual, learning, memory,  
76 linguistic, or thinking abilities” is defined as cognitive impairment [10]. Cognitive  
77 impairments associated with HIV have been reported in CLHIV [11–13], thus it may be  
78 assumed that CLHIV are at risk of presenting with auditory processing deficits.

79

80 Poor academic performance and/or school functioning and neurocognitive deficits have  
81 been reported in CLHIV [11,14–16]. The effects of HIV may not necessarily be as a direct  
82 consequence of the virus but may be due to the indirect consequences of living with a  
83 chronic disease or living with an adult who has the virus [11]. School performance may  
84 be affected as CLHIV may be more prone to illness, resulting in poorer school attendance  
85 due to sick days, or medical appointments [17]. In addition, living with an infected adult  
86 may have implications on socioeconomic status as HIV is more prevalent in lower  
87 socioeconomic households [18].

88

89 Lower socioeconomic status has also been associated with poorer learning outcomes  
90 and poorer performance on cognitive tests [19,20]. The effect of socioeconomic status on  
91 the brain and on cognition has been attributed to three possible mechanisms; namely (1)  
92 prenatal factors that can affect early brain development (e.g. poor nutrition during

93 pregnancy), (2) parental care issues that could affect neurodevelopment and (3) the level  
94 of stimulation in the home (e.g. availability of books) [21].

95

96 Assessing cognition is challenging as cognitive ability is not an isolated construct. It  
97 includes skills that underlie the processes of “perception, learning, memory,  
98 understanding, awareness, reasoning, judgment, intuition and language” [22]. The  
99 assessment tool should, therefore, be able to assess individuals across different contexts,  
100 and consideration should be given to the fact that the constructs being assessed may not  
101 be relevant for all cultures and across all languages [21]. For the purpose of this study,  
102 nonverbal intelligence was selected as the proxy for learning capacity as this construct is  
103 considered to be less affected by socioeconomic status and linguistic, cultural and literacy  
104 diversity [23]. Nonverbal IQ tests measure an individual's capacity to learn and problem  
105 solve, and is also known as fluid intelligence, as compared to crystallized intelligence  
106 which refers to the knowledge an individual has learnt [24]. The use of a nonverbal  
107 measure was therefore considered a valid method of measuring learning capacity in a  
108 sample of CLHIV and controls who spoke different languages and came from different  
109 contexts.

110

## 111 **METHODS**

112 *Ethics:* Approval for this research was obtained from Stellenbosch University Human  
113 Research Ethics Committee (S15/10/220). Both the Western Cape Department of Health  
114 and Western Cape Department of Education granted permission for the study to be  
115 conducted and permission was also obtained from the relevant tertiary hospital and

116 primary school. Written informed consent was obtained from all the children and their  
117 parents/caregivers.

118

119 *Study aims:* To investigate the association between HIV status, gender and language  
120 spoken at home and school, auditory processing skills and learning capacity.

121 *Sample:* This study investigated school learners aged 9 to 12 years who had confirmed  
122 HIV positive status (HIVP) or reported HIV negative status (HIVN). The sample was not  
123 age- or gender-matched.

124

125 *Sampling context:* One large tertiary metropolitan hospital in Cape Town provided access  
126 to paediatric HIV cases attending its Infectious Diseases Clinic (IDC). This hospital  
127 provided services for over 3.4 million people in surrounding socioeconomically-  
128 disadvantaged suburbs [25].

129

130 *Sampling:* The case children (HIVP group) were recruited at point of contact with the IDC  
131 in the participating hospital, and control children (HIVN group) were recruited from one  
132 school in the suburbs serviced by the participating hospital. Sampling participants from  
133 the hospital IDC, or from a school in the surrounding suburbs guaranteed homogeneity  
134 of sociodemographic status. Convenience sampling was applied for both groups, this  
135 being considered as the most efficient approach to deal with the complexities of  
136 recruitment in low socioeconomic circumstances (difficulty in contacting potential subjects  
137 when not attending health appointments or school, parent literacy, difficulty in accessing  
138 comprehensive records for random selection of subjects, parent suspicion of being



139 approached by researchers, stigma, constraints on attendance at appointments, being  
140 over-researched etc).

141

142 *Inclusion and exclusion criteria:* Girls and boys were eligible to be included if they had:  
143 (1) documented HIV-positive status or reported HIV-negative status; (2) were aged  
144 between 9 – 12 years; (3) had verbal proficiency in at least one of English, Afrikaans or  
145 an African language; (4) were enrolled in at least Grade 3 in a mainstream primary school  
146 and (5) had a parent or caregiver with the ability to understand and complete a written  
147 consent form. Exclusion criteria were: (1) HIV status not documented/reported; (2)  
148 diagnosed comorbid conditions causing cognitive impairment (e.g. neurological  
149 conditions) that could affect understanding of, and performance in, the assessment  
150 batteries; (3) diagnosed cognitive impairment (e.g. intellectual disability) that could affect  
151 understanding of and performance on the assessment test batteries; or (4) on a waiting  
152 list for, or enrolled, in a school for learners with special education needs.

153

154 *Recruiting HIVP children:* According to the IDC records at the participating tertiary  
155 hospital, 836 patients (adults and children) were managed at the clinic, at the end of  
156 February 2017. Of these, 412 were children (aged 0 to 18 years), with an estimated 110  
157 children in the target age range. Between June 2017 and November 2018, attempts were  
158 made to recruit all these children when they attended the IDC for their medical  
159 appointments. The recruitment process involved the researcher attending the IDC and  
160 identifying and recruiting appropriate children. On each of the paediatric clinic mornings  
161 (Monday to Wednesdays, 8h00 – 13h00), the researcher accessed the medical records

162 (folders) of all children with appointments for the particular day and identified potential  
163 candidates based on their date of birth. The parents/caregivers, who accompanied the  
164 child on the day, were approached and informed about the study. If they were interested,  
165 the child's eligibility was confirmed by questioning, and if parents/ caregivers and child  
166 consented, the child was enrolled in the study. Each family was offered a small  
167 reimbursement for travelling costs, to assist them to bring their child for the study  
168 appointment.

169

170 *Recruiting HIVN children:* Children were recruited from one local primary school from the  
171 surrounding area. Information pamphlets were distributed to all 162 children aged 9-12  
172 years, together with informed consent forms and the researcher's details. The school was  
173 considered as a Full-service school by the WCDoE, where the children's HIV status was  
174 known by the school. The school manager assisted the researcher in distributing  
175 research information only to children who were recorded as HIVN.

176 *Hypotheses:* In children with no hearing deficits:

- 177 1. HIV status is related to auditory processing performance and learning capacity,  
178 with HIVP status being associated with poorer performance;
- 179 2. Gender, and primary language spoken at home, or school, is unrelated to auditory  
180 processing performance and learning capacity; and
- 181 3. Auditory processing is strongly and positively correlated with learning  
182 performance.

183

184 *Demographic information:* Data was collected from clinic or school records as HIV status,  
185 gender, and language spoken at home and school.

186

187 *Screening for hearing loss:* All consenting children were tested for hearing loss using pure  
188 tone audiometry. The same test circumstances were unavailable for cases and controls.  
189 For cases, testing occurred in a soundproof booth in the hospital, using a GSI 61  
190 audiometer and circum-aural earphones. Air conduction thresholds were obtained at  
191 250Hz, 500 Hz, 1000 Hz, 2000Hz, 4000Hz, 8000 Hz as per conventional audiometry [26],  
192 for separate ears. For controls, testing occurred in a quiet venue at school, as a  
193 soundproof environment was re unavailable. Testing was completed using an  
194 Interacoustics AS608 screening audiometer, and circum-aural earphones. Air conduction  
195 thresholds were obtained at 250Hz, 500 Hz, 1000 Hz, 2000Hz, 4000Hz, 8000 Hz as per  
196 conventional audiometry [27], for separate ears. Due to differences in test conditions for  
197 cases and controls, different pure tone averages were used to determine normal hearing  
198 ( $\leq 15\text{dBHL}$  for cases,  $\leq 25\text{dBHL}$  for controls) [28,29].

199

200 *Learning capacity:* All children were assessed for learning capacity using the Test of  
201 Nonverbal Intelligence Fourth edition (TONI 4). According to Brown, Sherbenov and  
202 Johnsen [30], the TONI 4 measures aptitude, abstract reasoning and problem solving  
203 ability. The test was considered to be most suitable for the purposes of this study as it is  
204 not loaded with language and does not require the respondent to read, write, speak or  
205 even listen and can and can be used with children who are not proficient in English. The  
206 test items are arranged according to difficulty level (i.e. from easy to difficult) and,

207 according to the developers, performance is not influenced by familiarity with the items.  
208 The abstract nature of the items, as well, as the lack of language reduces the possibility  
209 of educational, cultural and experiential biases [30]. However, the instructions were given  
210 in the preferred language of the child, with the parent present. The parent/caregiver was  
211 provided with a written translation of the instructions and was requested to give these  
212 instructions to the child. Where literacy was a problem, the researcher explained the  
213 instructions to the parent with the aid of the written translation and the parent then  
214 transmitted the information to the child. The TONI-4 percentile score provided an  
215 indication of the percentage of the normative population that obtained a score equal to or  
216 below the score obtained by the participant [30].

217

218 *Working memory:* Only those children with normal hearing, proceeded to be assessed for  
219 the measures of memory. These tests were included based on the review of the position  
220 statements and clinical guidelines commenting on the impact on memory on auditory  
221 processing, as well as studies reflecting the association between working memory and  
222 learning difficulties [31].

223 - Subtests of the TAPS-3 [32]

- 224 ○ Number Memory Forward (NMF): The child has to listen to a series of digits  
225 and repeat the sequences verbatim.
- 226 ○ Number Memory Reversed (NMR): The child has to listen to a series of  
227 digits and say the sequence in reverse order.

228

229 *Auditory processing:* Only those children with normal hearing proceeded to auditory  
230 processing testing. The components of the test battery was based on the auditory skills  
231 that this study aimed to assess and was informed by a review of position statements and  
232 clinical guidelines on auditory processing [7,9,33–35].

233 The auditory processing test battery consisted of the following:

- 234 - Subtests of the SCAN 3C [36]
  - 235 ○ Gap Detection (GD)
  - 236 ○ Auditory Figure-Ground (+8 dB signal to noise ratio) (AFG)
  - 237 ○ Competing Words-Free Recall (CWFR)
- 238 - Subtest of the TAPS 3 [32]
  - 239 ○ Word Discrimination (WD)
- 240 - Laterality as measured by correct identification of ear that the stimulus was  
241 presented during the AFG test.

242 AFG, CWFR, WD, NMF and NMR (measured as percentage of total possible scores),  
243 and GD and laterality (measured in binary form).

244

245 *Data management:* Only those children with no hearing deficits were retained for the  
246 analysis reported in this paper. The percentage of total scores for the auditory processing  
247 and learning capacity variables (AFG, CWFR, WD, NMF, NMR, TONI 4) were converted  
248 into binary form by splitting them at the median value. Primary language spoken at home  
249 and school was recorded for testing purposes as English, Afrikaans or other African  
250 languages (these being combined because of small numbers). HIV status was reported  
251 as cases (HIVP) or controls (HIVN).

252

253 *Data analysis:* Factor analysis was first applied to the auditory processing measures  
254 (AFG, CWFR, WD, gap, laterality) and the learning capacity variables (TONI-4 NMF,  
255 NMR), to identify underlying composite latent variables. These variables were first tested  
256 for normality of distribution to ensure that they were appropriate for inclusion in factor  
257 analysis models. Spearman (1904) first developed the notion of factor analysis. Its key  
258 concept is that a latent (not measured) variable will underpin a number of observed  
259 (potentially correlated) variables because research subjects may express similar patterns  
260 of responses in the observed variables. In most instances, the latent factor is abstract,  
261 and therefore not readily measured. However, the abstract notion underpinning the latent  
262 factor may have multiple measurable elements, which, when combined, can provide a  
263 single estimate of the new (latent) variable. .Thus, the purpose of factor analysis is to  
264 analyse these patterns of responses, identify underlying latent factors, and use each  
265 latent factor as single measure, expressing a combination of observed variables. Factor  
266 analysis also weights item responses within each latent factor (called factor loadings).  
267 These can be combined and then expressed as an individual score for each person, as  
268 an estimate of the latent variable. Factor loadings can be interpreted in the same was as  
269 standardized regression coefficients. If an observed variable has a factor loading of, say,  
270 0.7 then it can be assumed that that observed variable has a correlation of 70% with the  
271 latent factor (a strong relationship). Conversely, if the loading is 0.2, the correlation of  
272 20% with the latent factor would be considered to be weak. On this assumption, the rules  
273 of correlation are applied when considering the factor loadings, as usually only those  
274 variables with loadings over 0.30 are considered as important within a latent variable [37].

275 Each factor captures an amount of the overall variance in the observed variables, and  
276 statistical programs which calculate factor analysis usually list factors in order of the  
277 amount of variation that each factor explains of the overall variance. The eigenvalue is a  
278 measure of how much variance in the observed variables is explained by one factor. As  
279 a rule of thumb, any factor with an eigenvalue greater than one explains more variance  
280 than a single observed variable.

281

282 The weighted auditory processing scores were combined into a new latent variable of  
283 per-child overall auditory process performance, and the weighted learning capacity  
284 scores were combined into a new latent variable of per-child overall learning capacity.  
285 This was calculated as the cumulative sum of the binary value (1,0) for each variable  
286 multiplied by the relevant weighing. Given that scores of 1 indicated poor performance,  
287 the higher the composite score, the poorer the child performed overall.

288

289 Influence of predictor variables: The influence of potential predictor variables (HIV status,  
290 gender, and primary language spoken at home or school) on the new (continuous  
291 measure) latent variables of auditory performance and learning capacity was assessed  
292 using Analysis of Variance models, with significance reported at  $p < 0.05$ . The association  
293 between the new latent variables of auditory performance and learning capacity was  
294 assessed using a univariate linear regression model, with the strength of the association  
295 reported as  $r^2$  value (significance  $p < 0.05$ ).

296 Univariate logistic regression models were also constructed to test the association  
297 between binary forms of the new (composite) latent variables of auditory processing and

298 learning capacity (reported as Odds Ratios (OR), 95% Confidence Intervals (95%CI). If  
299 a potential predictor variable was found to significantly influence the mean values of the  
300 composite auditory processing or learning capacity variables, its confounding effect was  
301 assessed by adding it to logistic regression models, and testing whether the Likelihood  
302 ratio  $\chi^2$  value changed significantly. This was an expression of the amount of variance  
303 in the model explained by the component variables. The significance of change was  
304 determined by whether the amount of exceeded the critical amount of change in the  $\chi^2$   
305 value for the number of degrees of freedom in the model.

306

## 307 **RESULTS**

308 *Sample descriptor:* This paper reports on the 43 children in the sample with no hearing  
309 loss (78.2% sample). There were 15 case children (34.9% sample), of whom 8 (53.3%  
310 of cases) were girls, and 28 control children (65.1%), of whom 15 were girls (53.3%).  
311 Figure 1 illustrates the sampling process.

312

313

314

315

316

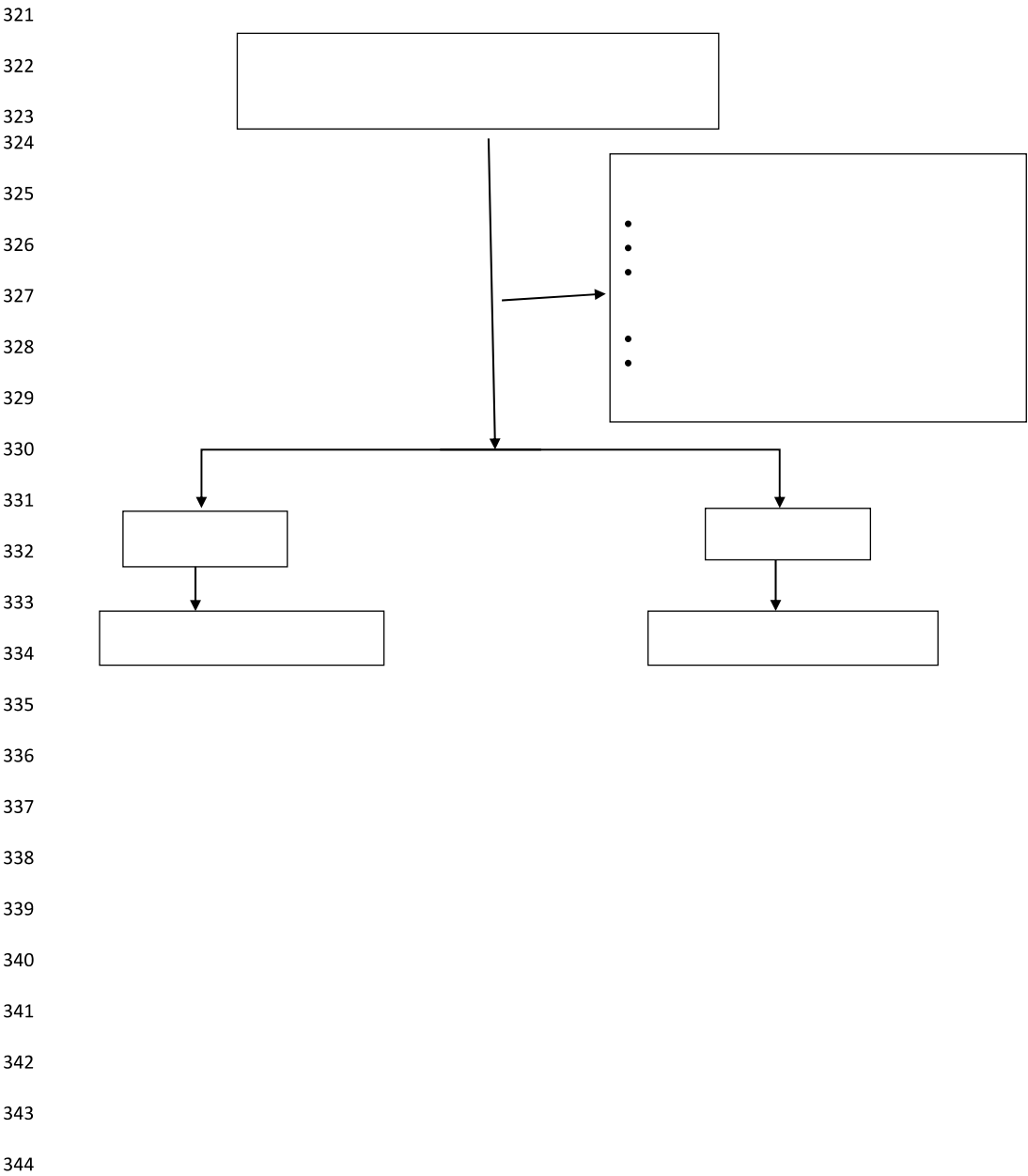
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319

320





cases; and 25% controls speaking an African language compared with 75% cases. Overall, approximately 1:5 children (20.9%) spoke a different language at home and school, reflecting 14.3% controls and 33.3% cases ( $p>0.05$ ). No English-speaking children reported a difference between home and school language, however, home-school language difference was found in five cases (one Afrikaans-speaker (20%), and four African language speakers (80.0%); and in four African speaking controls (100%).

Of the 14 cases on whom information on ART was available from hospital records, the mean percentage of lifetime exposure to ART was 73.4% (21.5%).

*Learning capacity and working memory:* Controls had significantly higher TONI 4 and NMR percentile scores compared with cases, but there was no difference in mean percentile scores for NMF between cases and controls (Table 1).

**Table 1.** Learning capacity and working memory scores for cases and controls

	Cases (n=15)	Controls (n=28)	P value ANOVA models
TONI percentile ranks	20.4 (10.1)	40.6 (19.2)	<0.05
Number memory forward (NMF) ranks	37.8 (27.1)	38.4 (26.7)	>0.05
Number memory backward (NMR) ranks	11.2 (11.9)	31.9 (23.9)	<0.05

a

*Factor analysis:* Latent 'composite learning capacity' was explained by one factor which included all three learning capacity measures (NMR ranked percent weighting = 0.79;

363 NMF ranked percent weighting = 0.62; TONI 4 ranked percent weighting = 0.71). The  
 364 mean per-child overall latent learning capacity score was 1.2 (SD 0.7; range 0 to 2.1),  
 365 with a significant difference between cases and controls (mean cases 1.6 (SD 0.5); mean  
 366 controls (0.9 (SD 0.7) ( $p < 0.05$ )).

367

368 **Table 2.** Means (SD) by HIV status, and linear measures of association of auditory  
 369 processing skills and learning capacity (considering only children with intact hearing)

Means	HIVP (n=15)	HIVN (n=28)	p value (ANOVA models)
<b>AFG%</b>	<b>2.2 (4.2)</b>	<b>9.5 (10.2)</b>	<b>0.007</b>
<b>CWFR%</b>	<b>5.9 (10.4)</b>	<b>20.4 (21.7)</b>	<b>0.01</b>
WD%	43.8 (28.7)	40.1 (21.4)	0.63
NMF%	39.0 (27.4)	40.3 (26.5)	0.89
<b>NMR%</b>	<b>15.3 (15.1)</b>	<b>31.9 (23.9)</b>	<b>0.03</b>
<b>TONI%</b>	<b>21.3 (9.8)</b>	<b>40.1 (19.7)</b>	<b>0.007</b>
Linear measures of association ( $r^2$ )	<b>With TONI%</b>		
<b>AFG%</b>	<b>0.113 (11.3%)</b>		
<b>CWFR%</b>	<b>0.177 (17.7%)</b>		
WD%	0.02		
	<b>With NMF%</b>		
AFG%	0.002		
CWFR%	0.001		
WD%	0.02		
TONI%	0.02		

	With NMR%		
<b>AFG%</b>	<b>0.104 (10.4%)</b>		
CWFR%	0.04		
WD%	0.01		
<b>TONI%</b>	<b>0.116 (11.6%)</b>		

370

371 *Auditory processing:* Twenty-one children of the sample (48.8%) presented with poor  
 372 auditory processing scores, comprising 11 cases and 10 controls (52.4%, 47.6%  
 373 respectively). Cases incurred a significantly greater risk of having poor auditory  
 374 processing scores compared with controls (OR 4.95 (95%CI 1.24-19.69). Not  
 375 surprisingly, the mean percentile scores for each of the auditory processing tests (AFG,  
 376 CWFR, WD) was generally lower for cases than controls (see Table 2). There was  
 377 modest evidence of an association between GD and HIV (OR 3.3 (95%CI 0.9-11.6)).

378

379 *Auditory processing and learning capacity (including working memory):* Significant  
 380 associations were found between the TONI percentile rank score and the percentile rank  
 381 scores for two auditory processing tests; namely AFG and CWFR. Significant  
 382 associations were also found between NMR and AFG, as well as between NMR and TONI  
 383 4. NMF was not significantly associated with any auditory processing tests or with TONI  
 384 4 (Table 2).

385

386 *Factor analysis:* There were two latent variables derived from factor analysis (explaining  
 387 58% and 42% respectively, of the total variance). The factor explaining the largest  
 388 percentage of variance included variables of AFG (weighting = 0.91); CWFR (weighting=

0.83); WD (weighting = 0.39); and laterality (weighting = 0.36). The second factor contained only one variable, GD (weighting = 0.75). The mean per-case score for the first latent variable was 0.50 (0.36) whilst for controls it was 0.29 (0.37). For the second latent variable, the per-case mean score was 1.74 (0.71) whilst for controls it was 0.96 (0.82)).

*Univariate association between composite auditory processing and learning capacity scores:* There was a significant and moderately-strong linear association between the continuous forms of these two latent variables without taking account of cases or controls ( $r^2=19.4\%$  ( $p<0.01$ )). However, when considering these variables in binary form, the crude association was non-significant (Odds Ratio (OR) 2.8 (95% Confidence Interval (CI) 0.8-9.4) (Likelihood Ratio 2.8 ( $p<0.05$ )).

*Influence of predictor variables:* Only HIV status produced significantly different means, when considering outcomes of composite auditory processing and learning capacity scores (See Table 3). The cases produced significantly higher scores than the controls (meaning that cases accumulated more poor scores in the component auditory processing and learning capacity composite measures). Gender, language spoken at home and differences between home and school language did not influence the mean component auditory processing or the learning capacity composite measures.

<<Table 3 about here>>

412 **Table 3.** Means (SD) of composite auditory processing and learning performance scores,  
 413 and significance from univariate ANOVA models

		Auditory processing composite means (SD)	<i>p value</i>	Learning capacity composite means (SD)	<i>p value</i>
Gender (degrees of freedom (df) =1)	Girls	1.8 (0.9)	0.05	1.1 (0.6)	<i>0.4</i>
	Boys	1.3 (0.9)		0.9 (0.8)	
Language at home (df=2)	English	1.1 (0.8)	0.05	0.7 (0.6)	0.05
	Afrikaans	1.8 (0.9)		1.2 (0.6)	
	African language	1.8 (0.8)		1.3 (0.7)	
Difference between primary home and school language (df=1)	No difference	1.6 (0.9)	<i>0.8</i>	1.1 (0.7)	<i>0.7</i>
	Difference	1.5 (0.8)		0.9 (0.5)	
HIV status (df=1)	Control	1.2 (0.8)	<b>&lt;0.001</b>	0.8 (0.7)	<b>&lt;0.001</b>
	Case	<b>2.2 (0.8)</b>		<b>1.5 (0.6)</b>	

414

415 *Association between composite learning capacity and composite auditory processing*  
 416 *variables:* The Crude Odds Ratio (COR) for the association between the auditory  
 417 processing and learning capacity composite measures (split at the median) was non-  
 418 significant (2.7 (95%CI 0.8-9.5)). Adjusting this by HIV status, the adjusted OR (AOR)  
 419 was significantly lower than the COR (1.8 (95%CI 0.5-7.5)), supported by a significant  
 420 change in the Likelihood ratio (6.6 (df=2)  $p < 0.05$ ). The AOR was also non-significant. The  
 421 wide confidence intervals potentially reflected the impact of small numbers in some cells.  
 422 *Lifetime exposure to ART:* There was some indication in the cases that the extent of exposure to  
 423 ARV influenced auditory processing and learning capacity, in particular in the NMF measure.  
 424 Table 4 outlines differences between children whose lifetime exposure was less than 75% (N=7),  
 425 compared with cases whose exposure was longer (N=8). There was a non-significant association  
 426 between gap detection and ARV lifetime exposure (OR 0.67 (95%CI 0.08 – 5.87)).

427

428 **Table 4.**

	<75% LT exposure	75+% lifetime exposure	
TONI ranked percent	21.25 (11.54)	19.42 (9.09)	>0.05
<b>NMF ranked percent</b>	<b>24.25 (18.12)</b>	<b>55.83 (27.78)</b>	<b>&lt;0.05</b>
NMR ranked percent	14.71 (14.02)	6.20 (6.26)	>0.05
AFG ranked percent	2.47 (5.51)	2.42 (3.39)	>0.05
CWFR ranked percent	4.42 (8.33)	9.21 (13.47)	>0.05
WD ranked percent	48.14 (25.96)	36.71 (33.30)	>0.05

429

430 **DISCUSSION**

431 This study provides new information in an area with scarce research to date, regarding  
 432 HIV status, auditory processing and learning capacity [5]. It reports on a sample of South

433 African children aged 9 to 12 years old, recruited from a low socioeconomic area in Cape  
434 Town. The findings supported all three hypotheses, that HIVP status is related to poorer  
435 learning capacity in children with and without hearing loss, and that HIVP status is related  
436 to auditory processing performance in children with no hearing deficits. Gender, and  
437 primary language spoken at home, or school, is unrelated to auditory processing  
438 performance and learning capacity; and auditory processing is strongly and positively  
439 correlated with learning capacity in children without hearing deficits. The findings also  
440 suggest that for case children with intact hearing, whose lifetime exposure to ARV was  
441 less than 75%, there may be an influence on number forward memory. These findings  
442 suggest that there are complex causal pathways for paediatric auditory processing, HIV  
443 status, ARV lifetime exposure and learning capacity, and that these require further  
444 investigation in larger samples [38].

445

446 In CLHIV, cognitive impairments may be caused by the HIV virus itself affecting the  
447 central nervous system (CNS) (primary HIV CNS disease), or by an opportunistic infection  
448 due to compromised immune system affecting the CNS (secondary CNS disease) [39].  
449 During acute infection, HIV enters the CNS through infected macrophages (immune cells)  
450 that cross the blood brain barrier, causing CNS infection and triggering immune activation  
451 [40]. Due to the CNS infection, inflammatory cytokines and neurotoxins are released by  
452 the macrophages. This results in neuronal damage leading to primary HIV CNS [39].  
453 Infants are particularly susceptible to neuronal damage, with resultant neurologic  
454 complications, as their blood-brain barrier is more permeable [41,42].

455



456 Although ART has resulted in a decrease in the prevalence of severe forms of CNS  
457 pathology, neurocognitive impairment continues to be seen in CLHIV [41]. According to  
458 Brahmbatt et al [15], despite the early initiation of ART, with complete viral suppression  
459 being achieved, mild to moderate cognitive impairment may still be observed. Ellis, Calero  
460 and Stockin [39] suggest that the continued presence of cognitive impairment may relate  
461 to the mechanism of the blood brain barrier, which has been seen to restrict the movement  
462 of antiretrovirals into the CNS, possibly reducing the efficacy of ART in the brain.

463

464 Our findings of high prevalence of poor auditory processing skills in children with HIV are  
465 similar to those reported by Romero et al. [43] (52.4% compared with 60%). Specifically,  
466 our HIVP children performed more poorly on tasks involving language (speech in noise  
467 tasks and dichotic listening) than the controls. Although no other study has reported on  
468 speech in noise results in CLHIV, Romero et al. [43] also reported difficulties with dichotic  
469 listening in CLHIV. The authors ascribed their results to attention, memory and problems  
470 with auditory figure ground skills. In addition to working memory, we would also suggest  
471 that cognitive ability (learning capacity), is an important factor to consider in CLHIV.  
472 Considering that: (a) auditory processing disorders are defined as “difficulties in the  
473 perceptual processing of auditory information in the central nervous system and the  
474 neurobiological activity that underlies that processing” (9) and that (b) HIV causes  
475 disruption in CNS activity, with subsequent neurocognitive impairment; cognitive ability  
476 and its effect on auditory processing skills [44] are important considerations when  
477 assessing CLHIV.

478

479 Our findings regarding learning capacity and HIV concurs with the growing number of  
480 studies, conducted in Africa, reporting on lower cognitive functioning in school-aged  
481 CLHIV [11,12,15,45]. According to Phillips et al. [13] , who conducted a systematic review  
482 of 22 articles and a meta-analysis of six of these articles, working memory, executive  
483 function and processing speed were the cognitive domains most notable affected. Our  
484 findings are in agreement with these reported findings on impaired working memory in  
485 CLHIV, as well as with those reported by Musindo et al. [11] and Boivin et al. [45] on the  
486 association between nonverbal intelligence and HIV.

487

488 Poverty has been suggested as a factor affecting cognition [17,46]. By controlling for  
489 socioeconomic status by recruiting all children from the one sociodemographic area, we  
490 believe that we have identified HIV status as an important factor in compromised auditory  
491 processing and non-verbal learning capacity. As all the children in our study lived in the  
492 same low socioeconomic area (surrounding the case catchment hospital), we assumed  
493 that they all had similar exposure to poverty, and the concomitant diseases that  
494 accompany such circumstances. Our sample also reflected expected local area statistics  
495 in terms of language spoken at school and home. This suggests that in our sample,  
496 exposure to HIV may be the mediating factor for auditory processing difficulties or learning  
497 capacity for our cases.

498

499 *Limitations:* The cross-sectional design of this study does not support inferences about  
500 causality, and the small sample size potentially influences the significance of our findings.  
501 Recruitment strategies sought a sample recruited from similar socioeconomic

502 backgrounds for cases and controls, however as the sample was recruited from only one  
503 tertiary hospital and its surrounding suburbs within the Cape Metropole, generalisability  
504 is limited. Likely systematic biases may have been introduced by the pragmatic,  
505 circumstantially-driven strategies which we had to employ to recruit children. Cases and  
506 controls could not be matched on variables such as diet, noise exposure, health status,  
507 home emphasis on learning, or history of ear infections. Our learnings were that whilst  
508 future studies should seek to recruit larger samples, using random selection, they would  
509 have to employ innovative recruitment approaches to deal with the difficulties of recruiting  
510 children in low socioeconomic areas, for research in this sensitive health area.

511

## 512 **CONCLUSIONS**

513 HIV status appears to be significantly associated with learning capacity in children aged  
514 9 to 12 years who have no hearing loss. Moreover, auditory processing is significantly  
515 associated with learning capacity in case and control children with no hearing deficit. The  
516 association between HIV, auditory processing and learning capacity has significant  
517 implications for educational policies, as children living with HIV may require additional  
518 support within the schooling system to overcome neurocognitive deficits. The findings  
519 have further implications when prioritising school assessments, as testing learning  
520 capacity may need to be prioritised above testing for auditory processing deficits to  
521 ensure that cognitive deficits are not the cause of underlying scholastic difficulties. The  
522 implications are that the learning difficulties faced by HIVP children may be multifactorial,  
523 and research is needed into the various factors that may impede children's engagement  
524 in learning opportunities.

525

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531

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## Appendix D

### Explanation of Potential Associations

**Explanation of Potential Associations:** In order to frame this study and determine the most appropriate study measures, we applied the Bradford Hill criteria for causality (Hill, 1965). These nine criteria provide opportunities to consider the research question and the proposed associations and to defend our choice of measures.

**Strength:** Observational studies show strong evidence supporting relationships between hearing loss and auditory processing (Halliday, Tuomainen, & Rosen, 2017) (Rohlf et al., 2017; van Wieringen et al., 2018); hearing loss and learning; auditory processing difficulties and learning; HIV and learning; as well as HIV and hearing loss (Ensink & Kuper, 2017; Smith et al., 2017). Limited evidence is available, supporting the relationship between HIV and auditory processing (Dawood, Klop, Olivier, Elliott, & Pillay, 2019). This is the area to which the findings of this dissertation will contribute. Collecting both auditory processing data, and hearing loss data in this study provided the opportunity to explore how these measures of auditory function present in children, and what impact they had.

CLHIV has historically missed many opportunities for schooling because of absenteeism due to ill health and medical care (Anabwani et al., 2016). Moreover, it is likely that CLHIV has one or more caregivers who also have HIV, and who may have died, or are unwell, leading to more reasons why the child may be absent from school (Harrison et al., 2017). In South Africa, CLHIV also tend to come from low socioeconomic areas (Bunyasi & Coetzee, 2017a) where nutrition and hygiene may be inadequate, there may be overcrowding at home, and the environment at home may not be conducive for learning (Scott, Schaay,

Schneider, & Sanders, 2017). This dissertation will provide more information about preteen children's capacity to learn and whether this differs between CLHIV and uninfected controls.

**Consistency:** The relationship in children between HIV and hearing loss has been demonstrated in a small number of studies (Buriti et al., 2013; Khoza-Shangase & Turnbull, 2009; Palacios et al., 2008; Taipale et al., 2011; Torre et al., 2012). What does the evidence say? The relationship between HIV and auditory processing difficulties has received less attention, and the evidence supporting this relationship is inconclusive. Although studies within the paediatric population are limited, Matas et al. (2008) found that children with HIV were poorer at localizing sound than children who were not infected with HIV.

There is a consistent body of knowledge that supports the relationship between the capacity to hear, the capacity to process the information that is heard (auditory processing) and the capacity to learn, with three systematic reviews providing the best current evidence for these associations (de Wit et al., 2016; Kuppler, Lewis, & Evans, 2013; Moeller, Tomblin, Yoshinaga-Itano, Connor & Jerger, 2007).

Neurocognitive disorders are one of the most common consequences of HIV, which occur despite active ART (Farhadian et al., 2017). The central nervous system (CNS) can serve as an anatomic reservoir for HIV and continued immune activation of macrophages and microglia in the brain can lead to central neurological signs and symptoms (Ellis et al., 2009). Although the central auditory system has centres with special functions (e.g., recognizing pitch and timing), the overall task of extracting meaning from the sound is distributed throughout the CNS (Kraus & Anderson, 2016). This suggests that processes producing diffuse damage to the CNS, such as HIV infection, could affect central auditory processing in multiple ways (Zhan et al., 2017). Studies in people with concussion show that this

generalized brain injury is reflected in performance on central auditory tasks (Kraus & Anderson, 2016).

**Specificity:** Poor auditory functioning is not the only construct associated with the inability to learn. Other factors include chronic illness (Compas et al., 2017), nutrition, socioeconomic status, sleep deprivation, and family support structures (Habibullah & Ashraf, 2013). The complexity of the impact of factors on a child's capacity to learn is not fully understood, thus for this dissertation, we needed to propose a defensible causal path involving HIV, hearing, auditory processing, and learning with clearly defined roles in the causal path.

**Temporality:** Many things can impact a child's capacity to learn, but it is unlikely that a lack of capacity to learn precedes hearing difficulties and auditory processing. However, disease processes such as HIV, TB, malaria, their sequelae, and the treatments for these diseases impact learning. In CLHIV, hearing loss is more likely to be conductive while in adults living with HIV, it is more likely to be sensorineural (Ensink & Kuper, 2017). This supports the evidence of ototoxicity of ART, with resultant sensorineural hearing. Furthermore, auditory processing difficulties in adults who have been using ART have been reported (Maro et al., 2014).

**Biological Gradient:** Not only is it likely that hearing loss and poor auditory processing difficulties in children are associated with suboptimal learning, but it is also likely that the longer (e.g., delay in intervention) and more profound the auditory functional difficulties, the more the capacity to learn will be impacted (Vohr et al., 2012). Moreover, when adults who have HIV use ART, there appears to be a dose-response, i.e., the longer the ART is being used, the higher the odds of having a form of hearing loss (Maro et al., 2014). In children and adults, lower CD4+ counts (compromised immune system) have been associated with hearing loss, as well as poorer auditory processing and cognitive skills. When PLHIV live with

comorbid diseases (e.g., multi drug-resistant TB), they are more likely to present with hearing loss than uninfected people (Hong, Budhathoki & Farley, 2018).

**Plausibility:** It is well established that children who cannot hear properly, or process sounds, are less able to learn than children without hearing difficulties (de Wit et al., 2016; Kuppler et al., 2013; Moeller et al., 2007). Hearing loss in all children is mostly due to middle ear involvement (Robb & Williamson, 2016). However, a middle ear infection is also associated with decreased immunity associated with HIV (Ensink & Kuper, 2017). Despite a decrease in opportunistic diseases, a history of middle ear disease (even if it has been resolved) is associated with later auditory proceeding difficulties (Khavarghazalani et al., 2016; Machado & Teixeira, 2018),

**Coherence:** The argument for coherence is similar to the one for consistency.

**Experiment:** It is known that, generally, antibiotics are effective for resolving middle ear infections (Robb & Williamson, 2016), and that children whose hearing improves, show improved learning outcomes (Vohr et al., 2012). However, auditory processing deficits may remain (Khavarghazalani et al., 2016; Machado & Teixeira, 2018). The effectiveness of ART in managing opportunistic infections for CLHIV is well known, as systemic infections such as pneumonia were generally the cause of death with HIV (B-Lajoie et al., 2016; Iroezindu, 2016). Despite ART, hearing loss prevalence and middle ear pathology continue to be reported, with approximately 33% of CLHIV presenting with hearing loss (Ensink & Kuper, 2017). However, this means that there are approximately 67% of CLHIV who have intact hearing and are not necessarily learning optimally (Devendra et al., 2013; Pufall et al., 2014). Thus, continuing concerns with the capacity to learn for CLHIV must be focused on more subtle areas of how they learn. This dissertation aims to understand more about how CLHIV

and uninfected peers, without hearing loss, process what they hear and how they learn from this.

**Analogy:** It is not possible with the current body of knowledge, to draw an analogy with other body systems or environmental circumstances.

## Appendix E

### HREC Approval



#### Approval Notice

##### Response to Modifications- (New Application)

22-Mar-2016  
Dawood, Gouwa G

**Ethics Reference #: S15/10/220**

**Title:** An analysis of auditory functioning and capabilities of children with HIV/AIDS living in low socio-economic communities.

Dear Mrs. Gouwa Dawood,

The **Response to Modifications - (New Application)** received on **22-Feb-2016**, was reviewed by members of **Health Research Ethics Committee 2** via Expedited review procedures on **22-Mar-2016** and was approved.  
Please note the following information about your approved research protocol:

Protocol Approval Period: **22-Mar-2016 -21-Mar-2017**

Please remember to use your **protocol number** (S15/10/220) on any documents or correspondence with the HREC concerning your research protocol.

Please note that the HREC has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

#### After Ethical Review:

Please note a template of the progress report is obtainable on [www.sun.ac.za/rds](http://www.sun.ac.za/rds) and should be submitted to the Committee before the year has expired. The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit.

Translation of the consent document to the language applicable to the study participants should be submitted.

Federal Wide Assurance Number: 00001372  
Institutional Review Board (IRB) Number: IRB0005239

The Health Research Ethics Committee complies with the SA National Health Act No.61 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 Part 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes 2004 (Department of Health).

#### **Provincial and City of Cape Town Approval**

Please note that for research at a primary or secondary healthcare facility permission must still be obtained from the relevant authorities (Western Cape Department of Health and/or City Health) to conduct the research as stated in the protocol. Contact persons are Ms Claudette Abrahams at Western Cape Department of Health ([healthres@pgwc.gov.za](mailto:healthres@pgwc.gov.za) Tel: +27 21 483 9907) and Dr Helene Visser at City Health ([Helene.Visser@capetown.gov.za](mailto:Helene.Visser@capetown.gov.za) Tel: +27 21 400 3981). Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. Ethics approval is required BEFORE approval can be obtained from these health authorities.

We wish you the best as you conduct your research.  
For standard HREC forms and documents please visit: [www.sun.ac.za/rds](http://www.sun.ac.za/rds)

If you have any questions or need further assistance, please contact the HREC office at 219389819.

## APPENDIX F

### Letter to Western Cape Department of Health

Ms Charlene Roderick

Assistant Director: Research

Department of Health

Western Cape

[Health.Research@westerncape.gov.za](mailto:Health.Research@westerncape.gov.za)

### REQUEST FOR PERMISSION TO CONDUCT RESEARCH IN HEALTH FACILITIES

Dear Ms Roderick

My name is Gouwa Dawood, and I am a student in the Division of Speech-Language Therapy, Stellenbosch University. The research I wish to conduct for my Doctoral degree involves the analysis of hearing functioning and capabilities in children with HIV/AIDS. This project will be conducted under the supervision of Dr Daleen Klop (Stellenbosch University) and Associate Professor Mershen Pillay (University of KwaZulu Natal).

I am hereby seeking your consent to research various health facilities. XXX Hospital will serve as the primary site, with all audiological assessments being conducted in the Audiology Clinic. The other health facilities will be approached to refer candidates for the study and to provide medical information for the relevant participants. All data collected in this study will be kept confidential, and data from individual children will not be shared with anyone other than my supervisors.

I have provided you with a copy of my proposal, which includes copies of the questionnaire and consent/assent forms to be used in the research process, as well as a copy of the approval letter which I received from the Stellenbosch University Human Research Ethics Committee (HREC). The completed application documents, as required by the Department of Health, are also included.

Upon completion of the study, I undertake to provide the Department of Health with a summary of the research findings. If you require any further information, please do not hesitate to contact me on 0727288022 or [gouwa@sun.ac.za](mailto:gouwa@sun.ac.za). Thank you for your time and consideration in this matter.

Yours sincerely,

Gouwa Dawood

Stellenbosch University



## Appendix G

## Permission from Western Cape Department of Education



Directorate: Research

[Audrey.wyngaard@westerncape.gov.za](mailto:Audrey.wyngaard@westerncape.gov.za)  
tel: +27 021 467 9272  
Fax: 0865902282  
Private Bag x9114, Cape Town, 8000  
[wced.wcape.gov.za](http://wced.wcape.gov.za)

**REFERENCE:** 20180523-2436**ENQUIRIES:** Dr A T Wyngaard

Mrs Gouwa Dawood  
28 Hurricane Street  
Factreton  
7405

**Dear Mrs Gouwa Dawood****RESEARCH PROPOSAL: AN ANALYSIS OF THE AUDITORY FUNCTIONING AND CAPABILITIES OF CHILDREN WITH HIV/AIDS LIVING IN LOW SOCIO-ECONOMIC COMMUNITIES**

Your application to conduct the above-mentioned research in schools in the Western Cape has been approved subject to the following conditions:

1. Principals, educators and learners are under no obligation to assist you in your investigation.
2. Principals, educators, learners and schools should not be identifiable in any way from the results of the investigation.
3. You make all the arrangements concerning your investigation.
4. Educators' programmes are not to be interrupted.
5. The Study is to be conducted from **19 July 2018 till 28 September 2018**
6. No research can be conducted during the fourth term as schools are preparing and finalizing syllabi for examinations (October to December).
7. Should you wish to extend the period of your survey, please contact Dr A.T Wyngaard at the contact numbers above quoting the reference number?
8. A photocopy of this letter is submitted to the principal where the intended research is to be conducted.
9. Your research will be limited to the list of schools as forwarded to the Western Cape Education Department.
10. A brief summary of the content, findings and recommendations is provided to the Director: Research Services.
11. The Department receives a copy of the completed report/dissertation/thesis addressed to:  
**The Director: Research Services**  
**Western Cape Education Department**  
**Private Bag X9114**  
**CAPE TOWN**  
**8000**

We wish you success in your research.

Kind regards.  
Signed: Dr Audrey T Wyngaard  
**Directorate: Research**  
**DATE: 24 May 2018**

## Appendix H

## Permission from a Tertiary Hospital



REFERENCE: Research Projects  
 ENQUIRIES: \_\_\_\_\_  
 TELEPHONE: \_\_\_\_\_

Ethics Reference: S16/02/022 220

**TITLE:** An analysis of auditory functioning and capabilities of children with HIV/AIDS living in low socio-economic communities.

Dear Mrs G Dawood

**PERMISSION TO CONDUCT YOUR RESEARCH AT \_\_\_\_\_ HOSPITAL.**

1. In accordance with the Provincial Research Policy and \_\_\_\_\_ Hospital Notice No 40/2009, permission is hereby granted for you to conduct the above-mentioned research here at \_\_\_\_\_ Hospital.
2. Researchers, in accessing Provincial health facilities, are expressing consent to provide the Department with an electronic copy of the final feedback within six months of completion of research. This can be submitted to the Provincial Research Co-Ordinator ([Health.Research@westerncape.gov.za](mailto:Health.Research@westerncape.gov.za)).

DR \_\_\_\_\_  
**MANAGER: MEDICAL SERVICES [RESEARCH CO-ORDINATOR]**

DR \_\_\_\_\_  
**CHIEF EXECUTIVE OFFICER**

Date: 13 October 2016

Private Bag X3, Tygerberg, 7505

## Appendix I

### Participant Information Leaflet and Informed Consent Form (Parents - Hospital)

**Title of the study:** An analysis of the hearing abilities of children with HIV/AIDS

**Reference Number:** S015/10/220

**Principal Investigator:** Gouwa Dawood

**Address:** Room 4065, 4<sup>th</sup> Floor  
Division of Speech, Language and Hearing Therapy  
Faculty of Medicine and Health Sciences  
Stellenbosch University  
Tygerberg

**Contact Number:** (021) 938 9494 / 072 278 8022

This information is provided to help you decide whether you and your child will be willing to take part in this clinical research study. Please read this form carefully and ask the study staff to explain any words or procedures you do not understand.

Dear Parent

My name is Gouwa Dawood and I am a student at Stellenbosch University. I would like to invite you and your child to take part in a study looking at Hearing Abilities in Children with HIV/AIDS. Before agreeing to participate in this study, it is essential that you fully understand what is involved. If you have any questions, which are not fully explained in this leaflet and consent form, do not hesitate to ask the study staff at any time.

If you agree and allow your child to take part in this study, you will be asked to sign and date this consent form. You will get a copy of the signed consent form to keep. You should only sign the consent form if all details of the study are apparent to you, if you are

willing to take part in this study with your child, and if you completely understand your and your child's rights as participants in this study.

**Why is this Study being Done?**

In this study, we want to learn how HIV may affect a child's hearing ability. We would like to do different hearing tests on children who have HIV or have been exposed to HIV and on children without HIV. We would like to assess if children who have HIV have a higher chance of developing hearing problems and to find out what these problems are.

**How Many Children will take Part and How Long will my Child be in this Study?**

Approximately 400 children will take part in the study. Your child will only need two study visits, and each visit will be approximately 1 hour and 30 minutes long. Completing the questionnaire will take approximately 30 minutes, and the other tests will be about 2 hours and 30 minutes. This time will be divided over the two sessions.

**Study Procedures**

If you agree to have your child take part in this study, you will need to come with your child to XXX hospital for two visits, where the following will take place:

We will ask you some questions about your child's medical, social, and school history, including previous or current illnesses and medication.

We will also ask you questions about your age, health, educational, and employment status.

We will ask your child's teacher questions about your child's learning and school behaviour.

We will perform the following examination on your child:

An examination of the outer ear and ear canal, using an otoscope, will be conducted.

The middle ear function will be assessed. An earplug will be placed in your child's ear, and they will feel slight pressure during the test. The child will not need to respond to anything during this test.

Hearing assessment where soft tones will be played through earphones. Your child will need to respond to these tones by raising their hand.

Inner ear function will be measured using distortion product otoacoustic emissions (DPOAEs). An earplug will be placed in your child's ear, and they will hear soft tones. Your child will be asked to remain quiet, and they will not have to respond to the tones.

Listening skills will be assessed. Your child will need to listen to speech sounds and respond where necessary.

If we notice problems with your child's ears, we may refer him/her for treatment and then ask you to come back to us for the hearing assessment after treatment.

We will not be taking any blood samples, but we will need to find out your child's HIV status, medical history, blood results, and treatment given from their doctor or your child's medical records.

If you are the mother of the child and you are HIV-infected, we would like to ask you questions about your CD4 counts, viral loads and medication during your pregnancy and birth of this child, or get this from your child's medical records if they are available.

### **What are the Risks to my Child when he/she Participates in the Study?**

None of the procedures we use are painful or dangerous, and all are used routinely in hearing clinics. Your child may feel worried or nervous during some of the tests, but we will reassure your child not to worry, and we will not put pressure on him or her. If your child is terrified or does not want the earplug in his/her ear, we will not do the test.

### **Are there Potential Benefits for my Child for being in the Study?**

There may be no direct benefits to you or your child; however, information from this study may help other children now or in the future. We will use the findings from this study for research purposes. If any of the tests show that your child has hearing problems that may

improve with help, we will discuss this with you. If you agree, we will then refer your child to an audiologist or doctor. No information about your child will be given to any doctors, hospitals, or schools unless you ask us and allow us to do so in writing.

### **What About Confidentiality?**

All medical information collected during the study will be treated as confidential and will be available only to staff members involved with this study who are directly involved in your child's care. Any information that is used for research or publication purposes or at scientific meetings will be kept confidential and will not have your name or your child's name recorded on it. Except if we see evidence of child abuse or neglect, it will be reported to the appropriate authorities, as required by law.

It is possible that the regulatory authorities, such as the Ethics Committees, may want to review the study documents at a later stage, in which case every effort will be made to protect your child's confidentiality.

### **Your Child's Participation is Voluntary**

Your child's participation in the study is voluntary. You can refuse to let him/her participate or stop his/her participation at any time that you choose. You and your child are also free not to answer any questions or to stop any task before it is finished.

Your child's withdrawal from the study will not affect his/her access to other medical care.

### **What Happens if your Child is Injured?**

A study-related injury or illness is one that occurs as a direct result of the study-specific procedures. If your child is injured as a result of being in this study, the study staff will give your child immediate necessary treatment for the injuries. If you think that your child has suffered a research-related injury, let the investigator know right away.

### **What are the Costs to You?**

Neither you nor your child's medical scheme will be expected to pay for the study-related visit or study procedures.

**Will you Receive any Payment for your Child's Participation?**

You will not receive payment for your child's participation in the study, although you will receive money for transport expenses to the clinic for each scheduled study visit.

**Ethical Approval**

This clinical study protocol has been submitted to and approved by the Faculty of Health Sciences Health Research Ethics Committee of Stellenbosch University and the faculty of Health Sciences Human Research Ethics Committee of the San Diego State University.

The study has been structured per the Declaration of Helsinki (2013), which deals with recommendations guiding doctors in biomedical research involving human participants.

I do not have any financial or personal interest in this organization that may bias my actions.

**What to do if you have Questions or Problems?**

If you have any questions now or in the future, you may contact me on 072 278 8022.

If you have questions or concerns about you or your child's rights as a research participant, you can contact the Chair of the Stellenbosch University Health Research Ethics Committee (021 938 9677). This independent committee is established to help protect the rights of research participants and gave written approval for the study protocol.

**Referral Option**

Please indicate below whether you want the study team to refer your child for help if we notice that your child has problems with the hearing testing.

☐ **YES**, I want you to refer my child for further help if problems are identified in the hearing testing.

☐ **NO**, I do not want you to refer my child for further help if problems are identified in the hearing testing.

### **Hearing Abilities in Children with HIV: Study Informed Consent Signature Page**

Name of participant: \_\_\_\_\_

*To parents/legal guardians:*

Have you read this information sheet about this study, or  
has someone read it to you and to your satisfaction?

Yes ☐ No ☐

Have you had an opportunity to ask questions and discuss  
this study?

Yes ☐ No ☐

Have you received satisfactory answers to all your  
questions?

Yes ☐ No ☐

Have you received enough information about this study?

Yes ☐ No ☐

Do you understand that you are free to withdraw your child  
from this study at any time?

Yes ☐ No ☐

Do you agree to let your child take part in this study?

Yes ☐ No ☐

#### **Parent/legal guardian:**

_____	_____	_____	<table border="1" style="display: inline-table; vertical-align: middle;"><tr><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td></tr></table>				
Name	Signature	Date	Time				

#### **Witness (if applicable):**

_____	_____	_____	<table border="1" style="display: inline-table; vertical-align: middle;"><tr><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td></tr></table>				
Name	Signature	Date	Time				



**A person conducting informed consent process:**

I am satisfied that the parent/legal guardian understands what the consent form is about and that his/her questions have been answered.

---

Name

---

Signature

---

Date

--	--	--	--

Time

## Appendix J

### Participant Information Leaflet and Informed Consent Form (Parents-School)

**Title of the study:** An analysis of the hearing abilities of children with HIV/AIDS

**Reference Number:** S15/10/220

**Principal Investigator:** Gouwa Dawood

**Address:** Room 4065, 4<sup>th</sup> Floor  
Division of Speech, Language and Hearing Therapy  
Faculty of Medicine and Health Sciences  
Stellenbosch University  
Tygerberg

**Contact Number:** (021) 938 9494 / 072 278 8022

This information is provided to help you decide whether you and your child will be willing to take part in this clinical research study. Please read this form carefully and ask the study staff to explain any words or procedures you do not understand.

Dear Parent

My name is Gouwa Dawood, and I am a student at Stellenbosch University. I would like to invite you and your child to take part in a study looking at Hearing Abilities in Children with HIV/AIDS. Before agreeing to participate in this study, it is vital that you fully understand what is involved. If you have any questions, which are not fully explained in this leaflet and consent form, do not hesitate to ask the study staff at any time.

If you agree and allow your child to take part in this study, you will be asked to sign and date this consent form. You will get a copy of the signed consent form to keep. You should only

sign the consent form if all details of the study are apparent to you, if you are willing to take part in this study with your child, and if you completely understand your and your child's rights as participants in this study.

### **Why is this Study being Done?**

In this study, we want to learn how HIV may affect a child's hearing ability. *We would like to do different hearing tests on children who have HIV or have been exposed to HIV and on children without HIV, who are 9 to 12 years of age.* We would like to assess if children who have HIV have a higher chance of developing hearing problems and to find out what these problems are.

### **How Many Children will take part and How Long will my Child be in this Study?**

Approximately 400 children will take part in the study. Your child will only need one study visit that will be approximately 1 hour long.

### **Study Procedures**

If you agree to have your child take part in this study, the study visit will be done at your child's school or at XXX Hospital (if you prefer), where the following will take place:

We will send you a questionnaire that asks you questions about:

Your child's medical, social and school history, including previous or current illnesses and medication

Your age, health, educational and employment status

We will ask your child's teacher questions about your child's learning and school behaviour.

We will perform the following examination on your child:

An examination of the outer ear and ear canal, using an otoscope, will be conducted.

The middle ear function will be assessed. An earplug will be placed in your child's ear, and they will feel slight pressure during the test. The child will not need to respond to anything during this test.

Hearing assessment where soft tones will be played through earphones. Your child will need to respond to these tones by raising their hand.

Inner ear function will be measured using distortion product otoacoustic emissions (DPOAEs). An earplug will be placed in your child's ear, and they will hear soft tones. Your child will be asked to remain quiet, and they will not have to respond to the tones.

Listening skills will be assessed. Your child will need to listen to speech sounds and respond where necessary.

If we notice problems with your child's ears, we may refer him/her for treatment and then ask you to come back to us for the hearing assessment after treatment.

### **What are the Risks to my Child when he/she Participates in the Study?**

None of the procedures we use are painful or dangerous, and all are used routinely in hearing clinics. Your child may feel worried or nervous during some of the tests, but we will reassure your child not to worry, and we will not put pressure on him or her. If your child is terrified or does not want the earplug in his/her ear, we will not do the test.

### **Are There Potential Benefits for my Child for being in the Study?**

There may be no direct benefits to you or your child; however, information from this study may help other children now or in the future. We will use the findings from this study for research purposes. If any of the tests show that your child has hearing problems that may improve with help, we will discuss this with you. If you agree, we will then refer your child to an audiologist or doctor. No information about your child will be given to any doctors, hospitals, or schools unless you ask us and allow us to do so in writing.

**What About Confidentiality?**

All medical information collected during the study will be treated as confidential and will be available only to staff members involved with this study who are directly involved in your child's care. Any information that is used for research or publication purposes or at scientific meetings will be kept confidential and will not have your name or your child's name recorded on it. Except if we see evidence of child abuse or neglect, it will be reported to the appropriate authorities, as required by law.

It is possible that the regulatory authorities, such as the Ethics Committees, may want to review the study documents at a later stage, in which case every effort will be made to protect your child's confidentiality.

**Your Child's Participation is Voluntary**

Your child's participation in the study is voluntary. You can refuse to let him/her participate or stop his/her participation at any time that you choose. You and your child are also free not to answer any questions or to stop any task before it is finished.

Your child's withdrawal from the study will not affect his/her access to other medical care.

**What Happens if your Child is Injured?**

A study-related injury or illness is one that occurs as a direct result of the study-specific procedures. If your child is injured as a result of being in this study, the study staff will give your child immediate necessary treatment for the injuries. If you think that your child has suffered a research-related injury, let the investigator know right away.

**What are the Costs to You?**

Neither you nor your child's medical scheme will be expected to pay for the study-related visit or study procedures.

**Will You Receive any Payment for Your Child's Participation?**

You will not receive payment for your child's participation in the study, although you will receive money for transport expenses to Tygerberg Hospital if you prefer to have the assessment done there.

### **Ethical Approval**

This clinical study protocol has been submitted to and approved by the Faculty of Health Sciences Health Research Ethics Committee of Stellenbosch University.

The study has been structured per the Declaration of Helsinki (2013), which deals with recommendations guiding doctors in biomedical research involving human participants.

I do not have any financial or personal interest in this organization that may bias my actions.

### **What to Do if You Have Questions Problems?**

If you have any questions now or in the future, you may contact me on 072 278 8022.

If you have questions or concerns about you or your child's rights as a research participant, you can contact the Chair of the Stellenbosch University Health Research Ethics Committee (021 938 9677). This independent committee is established to help protect the rights of research participants and gave written approval for the study protocol.

### **Referral Option**

Please indicate below whether you want the study team to refer your child for help if we notice that your child has problems with the hearing testing.

☐ **YES**, I want you to refer my child for further help if problems are identified in the hearing testing.

☐ **NO**, I do not want you to refer my child for further help if problems are identified in the hearing testing.

### **Hearing Abilities in Children with HIV: Study Informed Consent Signature Page**

Name of participant: \_\_\_\_\_

*To parents/legal guardians:*

Have you read this information sheet about this study, or  
has someone read it to you and to your satisfaction?

Yes ☐ No ☐

Have you had an opportunity to ask questions and discuss  
this study?

Yes ☐ No ☐

Have you received satisfactory answers to all your  
questions?

Yes ☐ No ☐

Have you received enough information about this study?

Yes ☐ No ☐

Do you understand that you are free to withdraw your child  
from this study at any time?

Yes ☐ No ☐

Do you agree to let your child take part in this study?

Yes ☐ No ☐

**Parent/legal guardian:**

_____	_____	_____	<table border="1" style="display: inline-table; vertical-align: middle;"><tr><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td></tr></table>				
Name	Signature	Date	Time				

**Witness (if applicable):**

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Name	Signature	Date	Time				

## Appendix K

### Participant Information Leaflet and Assent Form



**Title of the Research Project:** A hearing study in children

**Researchers Name(s):** Gouwa Dawood

**Address:** Room 4065, 4<sup>th</sup> Floor  
Division of Speech, Language and Hearing Therapy  
Faculty of Medicine and Health Sciences  
Stellenbosch University  
Tygerberg

**Contact Number:** (021) 938 9494 / 072 278 8022

#### **What is Research?**

Research is something we do to find new knowledge about the way things (and people) work.

We use research projects or studies to help us find out more about disease or illness. Research also helps us to find better ways of helping or treating children who are sick.

#### **What is this Research Project all About?**

The project is about looking at how school children hear. The project will look at the hearing problems that children, who are between the ages of 9 and 12 years, have.



**Why have I been Invited to Take Part in this Research Project?**

You have been invited because you are under 13 years old, and you have been coming to this hospital for assessments.

**Who is doing the research?**

My name is Gouwa Dawood, and I will be doing the research. I am a student at Stellenbosch University, and I am very interested in helping children who have hearing problems. I am doing this project so that I can see what kinds of hearing problems children have so that I know what to do to help them.

**What will happen to me in this Study?**

We will ask you to come and visit us at the clinic two times, and each visit will be about 1 hour and 30 minutes long. We will give you breaks during the visits so that you do not get tired. When you come for a visit, we will check your ears and ask you to listen to some noises and talking to check your hearing. We will need to put small earpieces in your ears.

**Can anything Wrong happen to me?**

The earpieces that we use to examine your ears may be a little uncomfortable. You should not feel any pain, and if you do, we will stop the test.

**Can anything Good happen to me?**

If you take part in this study, then we will know how well you are listening. You might not benefit yourself from being in the study. But you may help scientists learn about ways to help other children with hearing problems. If we find anything is wrong with your ears, we can make a plan on how to help you.

**Will anyone know I am in the Study?**

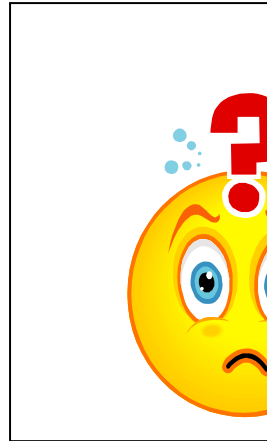
The study staff, your parents and your teacher will know that you are in the study, but your name will not be given to anyone else. We will give you a secret code that will be used on all papers.

**Whom can I talk to about the Study?**

If you want to talk about the study, you can talk to me. My phone number is 072 278 8022.

**What if I do not want to do this?**

You can say NO if you do not want to take part. If you say NO, we will not be angry and will care for you as before.



Do you understand this research study, and are you willing to take part in it?

YES

NO

Has the researcher answered all your questions?

YES

NO

Do you understand that you can pull out of the study at any time?

YES

NO

\_\_\_\_\_  
Signature of Child

\_\_\_\_\_  
Date

## Appendix L

## Case History Questionnaire

**Date:****General Information about child**

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---

Participant number:

Date of birth:

Age:

Gender:

Race:

Home language:

School language:

Birth rank of child:

(e.g. first of 3 children)

Person completing the  
questionnaire:(e.g., mother)

---

**General Information about Mother/Caregiver**

---

Date of birth:

Age:

Citizenship:

Race:

Home language:

Current marital status:

Highest level of education  
completed:Approximate annual income of  
the household:Number of people living in the  
house:

Current employment:

**Educational Information**

School:	<hr/>		Grade:	<hr/>
Teacher contact:	<hr/>		Race:	<hr/>
School performance:	<hr/>			
	Above average / Average / Below average			
Has your child repeated a grade? If yes, which grade?	<hr/>			
Is your child often absent? Why?	<hr/>			
Do you have any learning concerns?	<hr/>			
If yes, what are they?	<hr/>			
Does your child receive special education services?	<hr/>			
If yes, what services are these?	<hr/>			
Results from the most recent report:	<hr/>			

## Developmental/Medical/Family History

Please indicate if your child has experienced any of the following:

Premature birth		Hearing problems	
Problems before during or after birth		Speech-language problems	
Hyperbilirubinemia or jaundice		Sensory issues	
Congenital or perinatal infections		Autism spectrum disorder	
Meningitis or sepsis		Attention problems or hyperactivity	
Tuberculosis or Malaria		Syndromes	
Lack of oxygen at birth		Serious illness or accidents	
Mechanical ventilation		Ear problems or operations	
High fever		Currently takes medication	
Head or neck abnormalities		Delays in development	

If your child has experienced any of the above, please explain (also treatment and medications):

If anyone in your family has trouble hearing, please list their relationship to your child:

--

### Behaviours and Characteristics

Please indicate if your child shows any of the following:

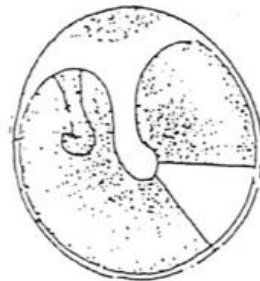
Sensitive to loud sounds		Disruptive or rowdy/loud	
Appears to be confused in noisy places		Temper tantrums	
Easily upset by new situations		Shy	
Difficulty following directions		Anxious/nervous	
Restless or problems sitting still		Lacks self-confidence	
Short attention span		Lacks motivation	
Impulsive		Disobedient	
Easily distracted		Inappropriate social behaviour	
Daydreams		Easily frustrated	
Forgetful		Tires quickly	
Asks for repetition		Difficulty understanding the meaning of words	
Reverses words, numbers or letters		Difficulty learning new concepts	
Prefers to play alone		Difficulty with reading	
Looks for attention		Difficulty expressing ideas	

Is there anything else that is important for me to know?

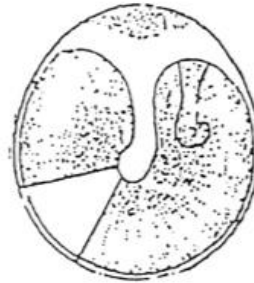
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## Appendix M

## Reference Form for Otoscopy



RIGHT EAR



LEFT EAR

LANDMARKS:

	<u>RE</u>	<u>LE</u>
Cone of light	.....	.....
Malleus	.....	.....
Umbo	.....	.....
Long Process of Incus	.....	.....
Pars Tensa	.....	.....
Annular Ligament	.....	.....

CERUMEN:

	<u>RE</u>	<u>LE</u>
Occluding	.....	.....
Excessive	.....	.....
Minimal	.....	.....
None	.....	.....

TYMPANIC MEMBRANE:

	<u>RE</u>	<u>LE</u>
Normal	.....	.....
Dull	.....	.....
Perforated (DI)	.....	.....
Plaque(DI)	.....	.....
Scarring(DI)	.....	.....
Grommets(DI)	.....	.....
Retracted	.....	.....
Meniscus(DI)	.....	.....

EXTERNAL CANAL:

	<u>RE</u>	<u>LE</u>
Normal	.....	.....
Reddened/Swollen	.....	.....
Foreign Body	.....	.....
Growth	.....	.....
Tube Extruded	.....	.....
Drainage (Describe)	.....	.....
Blood Present	.....	.....

COMMENTS: .....

.....

.....

\*DI = Draw In

## Appendix N

### OAE Protocol Scoring Rules (Grason-Stadler, 2009)

#### Addenda

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#### Protocol Scoring Rules

##### OAE 1: GSI Default

- Scores the test result as PASS when all three responses are at or above the Pass/Refer line and each response is individually scored as a Pass.
- Scores the test result as REFER when at least one response is below the Pass/Refer line and its response is individually scored as a Refer.
- Scores the test result as NOISE when at least one response is individually scored as noise.

##### OAE 4: 2 OUT OF 3

- Scores the test result as PASS when at least 2 out of 3 responses are at or above the Pass/Refer line and these 2 responses are individually scored as Pass.
- Scores the test result as REFER when at least 2 out of 3 responses are below the Pass/Refer line and these 2 responses are individually scored as Refer.
- Scores the test result as NOISE when at least 2 out of 3 responses are individually scored as Noise.
- If one response is PASS, one is REFER, and one is NOISE, the test result is scored as NOISE.



Selection of protocol OAE 1 versus OAE 4 depends upon the program's performance objective for hearing screening.



It is possible to save and print one ear with OAE 1 and the other ear with OAE 4.



## Appendix O

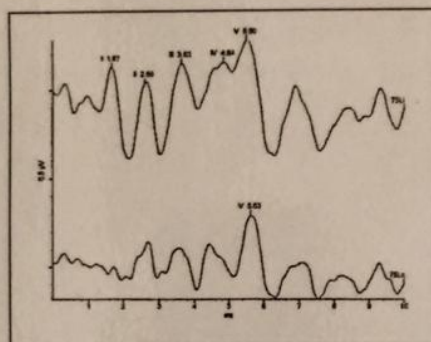
## Clinical norms for Audera system

**Retrocochlear (neurological) assessment****Table 2.** Absolute latencies [retrocochlear; 75dBnHL; rarefaction clicks]

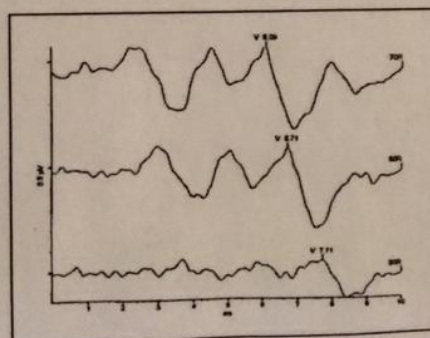
	MEAN	SD	RANGE
I (ms)	1.61	0.14	1.40 – 1.96
III (ms)	3.76	0.15	3.31 – 4.05
V (ms)	5.66	0.21	5.27 – 6.17

**Table 3.** Interpeak latencies [retrocochlear; 75dBnHL; rarefaction clicks]

	MEAN	SD	MEAN + 2SD	RANGE
I-III (ms)	2.15	0.15	2.45	1.79 – 2.46
III-V (ms)	1.89	0.15	2.19	1.52 – 2.13
I-V (ms)	4.03	0.21	4.45	3.62 – 4.48

**Audiological (threshold) assessment****Table 4.** The absolute latencies of peak V; three intensity levels.

	MEAN	SD	MEAN + 2SD	RANGE
V – 70dB (ms)	6.03	0.28	6.59	5.44 – 6.59
V – 50dB (ms)	6.80	0.38	7.56	6.02 – 7.92
V – 30dB (ms)	7.73	0.45	8.63	6.56 – 8.78



## Appendix P

## Data Collection Sheet – Medical File Review

Participant number:	
Date of birth:	Age:
Gender:	Race:
Gestation age:	Birth weight:
Congenital or perinatal infections:	
When was child's exposure to HIV?	Perinatal/postpartum (breast milk)
Did the child receive PMTCT?	
Child's current HIV status?	
Child's current ARV medication:	
(include a start date and whether the child is on 1 <sup>st</sup> , 2 <sup>nd</sup> or 3 <sup>rd</sup> line therapy)	
Child's previous ARV medication:	
(Include date started and date stopped. Also include whether the child was on 1 <sup>st</sup> , 2 <sup>nd</sup> or 3 <sup>rd</sup> line therapy)	

